**Federal Democratic Republic of Ethiopia**

**Ministry of Health**

# Poison Managment Hand Book

**EMRGENCY AND CRITICAL CARE DIRCTORATE**

**December 2016**

## Preface

Based on limited reports from studies done and from clinical experiences in emergency departments, poisoning and drug overdose is becoming a common problem in both pediatrics and adult Ethiopian population. Although the number varies, health facilities in Ethiopia are receiving and managing patients with poisoning, drug overdose and envenomation. Indeed, health professionals working in emergency departments and intensive care units are attempting to curb the problem despite limited facilities and capacities in the area. Nevertheless, the management approach being provided for poisoned patients in these facilities is not uniform. Moreover, there is lack of regular and extensive capacity building trainings on poison management. Hence, it is high time to prepare a poisoning management protocol in this country.

Therefore, the first edition of this *Protocol will* provide practical advice for the diagnosis and management of common poisonings, drug overdose and envenomation reported/encountered in healh facilities. The protocol will be used by physicians, nurses, pharmacists, health officers and laboratory professionals who are working in emergency departments and intensive care units. It will also be used to train health professionals on poison management. Poison information ceneters are also major users of this protocol to provide evidence based and timely information to professionals working in emergency departments and intensive care units. The *protocol* is divided into two sections. Section I takes the reader through initial diagnosis and general approach of poison management. Section II provides detailed information for common poisons and their management.

Dr Helena Hailu, (MD)

Director, Emergency and Critical Care Directorate

## Acknowledgement

The Federal Democratic Republic of Ethiopia Ministry of Health acknowledges the following individuals and their organizations for their participation in technical working groups for their contribution to the development of this Protocol.

Further more, the Ministry of Health would like to appreciate the Office of Research and Technology Transfer, School of Medicine, School of pharmacy, College of Health Sciences, Addis Ababa University for facilitating the review process.

Finally, the Ministry of Health extends special thanks to the American International Health Alliance (AIHA)/Twining Center for their financial support in the preparation of this protocol.

## Authors

Ephrem Engidawork (PhD), Associate Professor of Pharmacology
School of Pharmacy, College of Health Sciences, Addis Ababa University
Email: ephrem.engidawork@aau.edu.et, ephrem.engidawork@gmail.com
Tel: +251-911-408336

Tigist Bacha (MD, MPH), Consultant Pediatric Emergency and Critical Care Specialist
Assistant Professor of Pediatrics and Child Health
School of Medicine, College of Health Sciences, Addis Ababa University
Email: tigistbacha@yahoo.com
Tel: +251-911-676304

Sofia Kebede (MD), Emergency Medicine Specialist
Assistant Professor of Emergency Medicine
School of Medicine, College of Health Sciences, Addis Ababa University
Email: sofia_kebede@yahoo.com
Tel:+251-911-524442

Belete Ayalneh (BPharm, MPharm), Clinical Pharmacist
Lecturer, School of Pharmacy, College of Sciences, Addis Ababa University
Email: belete.ayalneh@aau.edu.et
Tel: +251-912-052782

**Reviewers**

Dr Aklilu Azaj (MD, Internist)
Associate professor of adult emergency medicine
School of Medicine, College of Health Sciences, Addis Ababa University
Email: akliluem@gmail.com

Dr. Teshome Nedi, (PhD)
Assistant Professor of Pharmacology

School of Pharmacy, College of Health Sciences, Addis Ababa University
Email: teshnm@yahoo.com

Dr. James Seveson (MD), Pediatrician
Associate professor of Emergency medicine
University of Wisconsin, USA
Email: Jes@medicine.wisc.edu

Dr. Legesse Chelkeba (PhD)
Assistant Professor of Clinical Pharmacy
Department of Pharmacy, College of Health Sciences, Jimma University
Email: bhailemeskel@howard.edu

Dr. Alan Mottram (MD), Medical Toxicology Subspecialty
Assistant Professor of Emergency Medicine
School of Medicine and Public Health, University of Wisconsin, USA
Email: armottram@medicine.wisc.edu

## Consltative workshop participants:

| | | |
|---|---|---|
| 1. | D/r Yonatan Gary | St. Paule/ AaBET |
| 2. | Sr. Emebet Teshager | FMOH, Emergency and Critical care Directoret |
| 3. | Ato. Tolosa Dida | St. Paule/ AaBET |
| 4. | Ato Getachew Regassa | Crop Life Ethiopia |
| 5. | Dr Yiblital Mekonen | FMOH, Clinical Service Directoret |
| 6. | Dr Selam | St Peter hospital |
| 7. | Dr Ermias Abraham | St Peter hospital |
| 8. | Sr. Bethelehem Shiferaw | FMOH, Emergency and Critical care Directoret |
| 9. | Ato. Getahun Tefera | Blacklion hospital |
| 10. | Ato. Million Negasa | Blacklion hospital |

## Table of Contents

## List of abbreviations and accronyms

| | |
|---|---|
| 2,4-D | 2,4-dichlorophenoxyacetic acid |
| ABC | Airway, Breathing and Circulation |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AV | Atrioventricular |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CNS | Central Nervous System |
| CPK | Creatinine Phosphokinase |
| CT | Computed Tomography |
| D5W | 5% dextrose in water |
| ECG | Electrocardiographic |
| ED | Emergency Department |
| FDA | Food and Drug Administration |
| GABA | ϒ-aminobutyric acid |
| GI | Gastrointestinal |
| H1 | Histamine 1 |
| H2 | Histamine 2 |
| Hcg | Human chorionic gonadotrophin |
| IM | Intramuscular |
| INH | Isoniazide |
| INR | International Normalized Ratio |
| IV | Intravenous |
| LP | Lumbar Puncture |
| MAO | Monoamine Oxidase Inhibitors |
| MRI | Magnetic Resonance Imaging |
| NAC | N-acetylcysteine |
| NSAIDs | Nonsteroidal anti-inflammatory drugs |
| PT | Prothrombin time |
| RNA | Ribonucleic acid |
| VD | Volume of Distribution |
| WHO | World Health Organization |

# Chapter 1: General Evaluation and Treatment

## 1.1 Introduction

Poisoning is an exposure to an amount of substance that is likely to produce untoward effects in an individual. There are six basic modes of exposure to poisons: ingestion, ocular exposure, topical exposure, envenomation, inhalation, and transplacental exposure. Poisonings may be the result of acute or chronic exposures and it is common to children and adults. The most important difference between the pediatric and the adult profile by type of agent is in the higher percentage of cases in which psychopharmacologic drugs (sedatives, tranquilizers, and antidepressants) cause poisoning in adults and the much higher frequency of exposures to household and personal care products and plants in children.

The clinical effects encountered in poisoned patients are dependent on numerous variables, such as dose, length of exposure time, and pre-existing health of the patient. The prognosis and clinical course of recovery of a patient poisoned by a specific agent depends largely on the quality of care delivered within the first few hours in the emergency setting. Poisoning can present with various clinical symptoms, including abdominal pain, vomiting, tremor, altered mental status, seizures, cardiac dysrhythmias, and respiratory depression. These may be the only clues to diagnosis when the cause of toxicity is unknown at the time of initial assessment and management. Fortunately, in most instances, the drug or toxin can be quickly identified by a careful history, a directed physical examination, and commonly available laboratory tests.

Attempts to identify the poison should never delay life-saving supportive care. If poisoning is recognized early and appropriate supportive care is initiated rapidly, majority of the patient outcomes will be good. Once the patient has been stabilized, the care provider needs to consider how to minimize the bioavailability of toxin not yet absorbed and other measures to enhance elimination are necessary. The goal of this chapter is to introduce the general approach for evaluation and appropriate management of a poisoned patient.

## 1.2 Epidemiology

Accidental and intentional poisoning remains a major cause of morbidity, mortality and and health care expenditure worldwide. The global incidence of poisoning is not known. It may be

speculated that up to half a million people die each year as a result of various kinds of poisoning. In the US in the year 2014, 2,165,142 human exposures were reported, 9% per year since 2000. The top 5 substance classes most frequently involved in all human exposures were analgesics (11.3%), cosmetics/personal care products (7.7%), household cleaning substances (7.7%), sedatives/hypnotics/antipsychotics (5.9%) and antidepressants (4.4%). Sedative/Hypnotics/ Antipsychotics exposures as a class increased most rapidly (2,368 calls (12.2%)/year) over the last 13 years for cases showing more serious outcomes. Rates of poisoning cases among Emergency Department (ED) patients appear similar in other industrialized nations (Mowry, 2015).

WHO estimated that there were 16, 500 deaths in 2012 from unintentional poisoning in 16 African countries. In addition, unintentional poisoning caused the loss of 1 128 500 years of healthy life (disability adjusted life years, DALYs) in these countries. These figures underestimate the true impact of poisoning since they do not include intentional self-poisoning or poisoning due to snakebite. It has been estimated, for example, that there are in the order of 7800 deaths per year in Africa due to deliberate ingestion of pesticides and between 1400 and 10 000 deaths from snakebite in eastern sub-Saharan Africa (WHO, 2012).

Although there are few studies done on poisoning in Ethiopia, acute poisoning is an important problem. Out of 116 adult patients presented with poisoning to Tikur Anbessa Specialized Hospital (TASH) from January 2007 to December 2008, females outnumbered males and mean age was 21 years, most being (96.5%) intentional self-harm poisonings. Household cleansing agents were the leading causes (43.1%) followed by organophosphates (21.6%) and phenobarbitone (10.3%) (Mekonnen and Azaji, 2011).

A study done on childhood poisoning in four hospitals located in Addis Ababa showed that it is not an uncommon problem and most of the children were poisioned with drugs prescribed for themselves or family. Most of the incidents were unintentional and occurred at home (Bacha and Tilahun, 2015). Another study done in Gondar University teaching hospital indicates that acute poisoning accounts for 0.45% of emergency admissions. Organophosphates, rat poison and alcohol were implicated in majority of the cases for suicidal as well as para-suicidal intentions (Abula and Wondmikun, 2006).

## 1.3 General approach

The general approach to the diagnosis and management of the poisoned patient can be described using a two-pronged model as depicted in Fig.1.1 as well as by the approach outlined in Box 1.1. The left-sided prong begins with basic emergency medical care-the ABCs (airway, breathing, circulation). In most potentially poisoned patients, a rapid blood glucose measurement should be obtained and any derangements corrected. Supplemental oxygen, naloxone and thiamine should be considered in the appropriate cases and situations. The various methods of decontamination should be considered in any poisoned patient. The exact method used should be based on each individual clinical situation.

Once a poisoning has been identified, methods of enhanced elimination should be considered. Focused therapy involves antidote administration when appropriate or aggressive supportive care tailored to the poison in question. Finally, when treating any poisoned patient, it is prudent to consider early consultation with a toxicology service or local poison control center for further guidance.The right-sided prong on the diagram focuses on obtaining the poisoning and other patient history, performing a focused physical examination with attention to toxidrome recognition, and deciding on the appropriate diagnostic tests to be performed. The two prongs often occur simultaneously and are integral to the diagnosis and management of a poisoned patient.

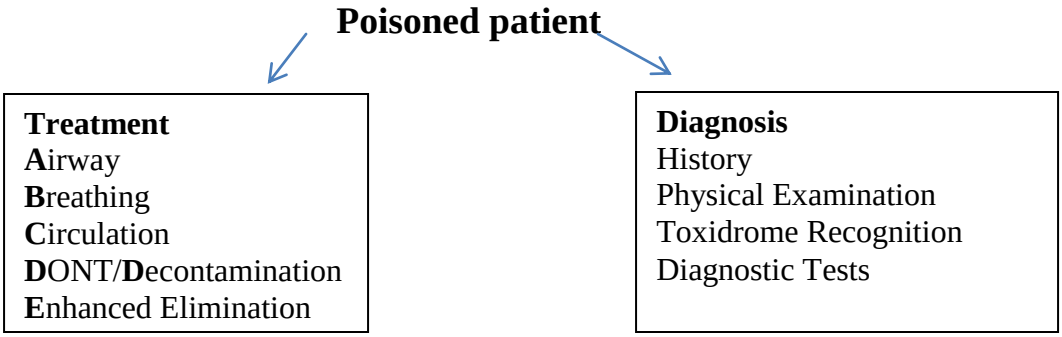


**Fig 1.1**: The two pronged approach to the poisoned patient: DONT stands for dextrose, oxygen, naloxone, and thiamine. It applies in case of uknown poisoning with unconsciousness and coma. Treat hypoglycemia with IV dextrose (glucose). Patients at risk of Wernicke's encephalopathy also require thiamine, but do not require that it be administered before the dextrose. Altered mental status, when hypoglycemia cannot be excluded, is an indication for IV dextrose. Supplemental oxygen, thiamine, glucose, and naloxone are often administered empirically as a cocktail in cases of altered mental status.

**Box 1.1:** General approach to acute poisoning

| | |
|---|---|
| i) Resuscitation<br>– Airway<br>– Breathing<br>– Circulation<br>– Seizure control<br>– Correct hypoglycaemia<br>– Correct hyperthermia<br>– Resuscitation antidotes | ii) Risk assessment<br>iii) Supportive care and monitoring<br>iv) Investigations<br>– Serum level (paracetamol, alcohol, aspirin<br>– ECG<br>v) Decontamination<br>vi) Enhanced elimination<br>vii) Antidotes<br>viii) Disposition |
| | |

## 1.4 Diagnosis of poisoning

### 1.4.1 History taking

History taking should include the type of toxin or toxins, time of exposure (acute versus chronic), amount taken, and route of administration (i.e., ingestion, intravenous, iv, or inhalation). It is also important to understand why the exposure occurred (accidental, suicide attempt, euphoria, or therapeutic misadventure) and whether there is history of psychiatric illness or previous suicide attempts. Furthermore, it is important to inquire about all drugs taken, including prescription, over-the-counter medications, vitamins, and herbal preparations as well as the nature and progression of signs and symptoms. If unavailable from the patient, information solicited from family and friends may also prove helpful, acting in the patient's best interest. Further history can be obtained by consulting the patient's other physicians or by obtaining old medical records. In the case of an occupational exposure, one should obtain a description of the work environment and contact people at the site for relevant information. Information regarding specific toxins may also prove useful.

### 1.4.2 Physical examination

In the emergency setting, performing an overly detailed physical examination is a low priority compared with patient stabilization. A directed examination can, however, yield important diagnostic clues. Once the patient is stable, a more comprehensive physical examination can reveal additional signs suggesting a specific poison. One should take note also that a dynamic change in clinical appearance over time may be a more important clue than findings on a single

examination. The following physical examinations might help to deduce the class of drug or toxin implicated in the poisoning.

- **Vital sign**: detecting signs such as tachycardia, hyperthermia, and hypotension through addressing the patient's vital sign help in making the differential diagnosis (Box 1.2).
- **Neurologic examination**: a systematic neurologic evaluation is important, particularly with patients exhibiting altered mental status. In contrast to the patient who has structural brain injury, the patient who has a toxic-metabolic cause of coma may exhibit ''patchy'' neurologic impairment. Toxicologic causes of coma rarely cause focal neurologic deficits. Seizures are common presentation of an unknown overdose, and the list of toxins that can induce a convulsion is lengthy. Classic pupillary findings include miosis (opioids, cholinergics, carbamates, clonidine, organophosphates, Phenotiazines, Sedatives-hypnotics) and mydriasis (sympathomimetics, anticholinergics, Withdrawal syndrome). Nystagmus suggests phenytoin, along with carbamazepine, lithium, ethanol, barbiturates, and sedative hypnotics. Vertical nystagmus largely represent brain stem lesion. Optic neuritis and vision loss, although seen in multiple sclerosis, may indicate advanced methanol poisoning. Other general neurologic signs include fasciculations (organophosphate poisoning), rigidity (tetanus and strychnine), tremors (lithium and methylxanthines), speech-mumbling (anticholinergics), and dystonic posturing (neuroleptic agents).
- **Skin:** a careful examination of the skin should be performed. The absence of diaphoresis is an important clinical distinction between sympathmimetics and anticholinergics. Bullous lesions may be associated with sedative-hypnotic drug-induced coma, but are classically described with barbiturate poisoning. Such lesions could also be indications of rhabdomyolysis or the development of compartment syndrome. A common skin finding is the presence of track marks, suggesting iv or subcutaneous (sc) opiate or cocaine abuse. Blue skin indicates methemoglobinemia or hypoxia; red skin may suggest niacin or boric acid exposure.

**Box 1.2**: Diagnosis of toxicity based on vital sign

- Hypothermia (COOLS)
  - **C**arbon monoxide
  - **O**pioids
  - **O**ral hypoglycemic, Insulin
  - **L**iquors (alcohol)
  - **S**edative-hypnotics
- Hyperthermia (NASA)
  - **N**euroleptic malignant syndrome, nicotine
  - **A**ntihistamines
  - **S**alycilates, Serotonin syndrome, sympathomimietcs
  - **A**nticholinergics, antidepressants, antipsychotics
- Hypotension (CRASH)
  - **C**lonidine, calcium channel blockers
  - **R**odenticides (arsenic, cyanide containing)
  - **A**ntidepressants, aminophilline, antihypertensives
  - **S**edative-hypnotics
  - **H**eroine or other opioids
- Bradycardia ( PACED)
  - Propranolol (β-blockers), Opiates
  - Anticholinergic drugs, antiarrythmics
  - Clonidine, calcium channel blockers
  - Ethanol and other alchols
  - Digoxin, digitalis
- Tachycardia ( FAST)
  - Free base or other forms of cocaine
  - Antihistamines, anticholinergics, alcohol withdrawl
  - Sympathomimetics (Cocaine, caffine, amphetamine)
  - Theophylline, TCAs

- **Odor:** some poisons produce odors characteristic enough to suggest the diagnosis, such as oil of wintergreen (methylsalicylates) or garlic (organophosphate insecticides, arsenic). Some odors may be more subtle and cannot be detected by a sizable number of the population, such as the freshly mowed hay smell of phosgene or the bitter-almond scent associated with cyanide. Certain odors may be overpowering and easily noted by anyone managing the patient. For example, sulfur dioxide and hydrogen sulfide produce a noxious rotten-egg smell.

### 1.4.3 Toxidromes

Identification of the constellation of signs and symptoms that define a specific toxicologic syndrome, or "toxidrome", may narrow a differential diagnosis to a specific class of poisons. Descriptions of selected toxidromes may be found in Table 1.1.

**Table 1.1:** Toxidromes associated with drug overdoses

| Toxidrome | Site of action | Sign and symptoms |
|---|---|---|
| Opioid (codein, morphine) | opioid receptor | Miosis, respiratory depression, central nervous system depression, Hypothermia, bradycardia, decreased bowel sounds |
| Anticholinergic (Atropine, *Datura* spp., antihistamines, antipsychotics) | muscurinic acetylcholine receptors | altered mental status, sedation, hallucinations, mydriasis, dry flushed skin, dry mucous membranes, decreased bowel sounds and urinary retention, hyperthermia,Seizures, arrhythmias, rhabdomyolysis |
| Sedative-hypnotic (Benzodiazepines, Barbiturates) | gamma-aminobutyric acid receptors | Central nervous system depression, ataxia, dysarthria Bradycardia, respiratory depression, normal pupils |
| Sympathomimetic (Amphetamines, Cocaine Cathinones) | alpha and beta adrenergic receptors | Agitation, tachycardia, hypertension, hyperpyrexia, diaphoresis, mydriasis, Seizures, acute coronary syndrome |
| Cholinergic (Organophosphate and carbamate insecticides) | nicotinic and muscarinic acetylcholine receptors | altered mental status, bronchospasm, diarrhea, Salivation, lacrimation, diaphoresis, vomiting, urination, bronchorrhea, muscle fasciculations, weakness Miosis/mydriasis, bradycardia, seizures |
| Serotonin syndrome (SSRIs, MAOIs, Tricyclic antidepressants, Amphetamines, Fentanyl St. John's wort) | serotonin receptors | altered mental status, hyperthermia, hyperreflexia and hypertonia (>lower limbs), clonus, tachycardia, diaphoresis, Hypertension, flushing, tremor |
| Salicylate (Aspirin, methyl salicylate) | Cox inhibitor | Altered mental status, respiratory alkalosis, metabolic acidosis, tinnitus, tachypnea, tachycardia, diaphoresis, nausea, vomiting Hyperpyrexia (low grade) |
| Neuromuscular malignant (Antipsychotics) | Dopamine receptors | Severe muscle rigidity, hyperpyrexia, altered mental status Autonomic instability, diaphoresis, mutism, |

| | | |
|---|---|---|
| | | incontinence |
| Hypoglycemic (Sulfonylureas, Insulin) | | Altered mental status, diaphoresis, tachycardia, hypertension<br>Dysarthria, behavioral change, seizures |
| Extrapyramidal (Risperidone, haloperidol, phenothiazines) | | Dystonia, torticollis, muscle rigidity<br>Choreoathetosis, hyperreflexia, seizures |
| Ethanolic (Ethanol) | | Central nervous system depression, ataxia, dysarthria, odor of ethanol |

Many toxidromes have several overlapping features and toxidrome findings may be affected by individual variability, comorbid conditions, and co-ingestants. In addition, while toxidromes may be applied to classes of drugs, some individual agents within these classes may have one or more toxidrome findings absent. Nevertheless, when accurately identified, the toxidrome may provide invaluable information for diagnosis and subsequent treatment.

### 1.4.4 Laboratory tests

In patients whose history is generally unreliable or in unresponsive patients where no history is available, the clinician may gain further clues as to the etiology of poisoning by responsible diagnostic testing. When a specific toxin or even class of toxins is suspected, requesting qualitative or quantitative levels may be appropriate if necessary for diagnosis and treatment. Several simple, readily available laboratory tests may provide important diagnostic clues in the symptomatic overdosed patient. These include measurements of complete blood count, electrolytes, liver function test, blood urea nitrogen, creatinine, serum glucose, a measured bicarbonate level, and arterial blood gases. If the patient is a female of child-bearing age, a pregnancy test is essential because these patients often overdose for suicidal or abortifacient reasons. To check for anion gap metabolic acidosis, calculate the anion gap using serum mEq/L measurements (Equation 1):

Equation 1: $Na – (Cl + HCO3)$

Although 8 to 16 mEq/L is traditionally accepted as the normal range for an anion gap, the measured and calculated anion gap can vary considerably. When a patient presents with an elevated anion gap, the approach METAL ACID GAP assists in identifying most of the common toxic causes (Box 1.3). In addition, knowledge of the dynamic relationship between the increase

in anion gap and the decrease in bicarbonate is also important (ΔAG - ΔHCO3). If positive and greater than 6, a metabolic alkalosis is usually present. A difference of less than 6 suggests that a hyperchloremic acidosis is present.

An increase in the anion gap beyond an accepted normal range accompanied by a metabolic acidosis, represents an increase in unmeasured endogenous (*e.g.* lactate) or exogenous (*e.g.* salicylates) anions. It is therefore imperative that clinicians admitting poisoned patients initially presenting with an increased anion gap metabolic acidosis investigate the etiology of that acidosis. Many symptomatic poisoned patients may have an initial mild metabolic acidosis upon presentation due to the processes resulting in the elevation of serum lactate. However, with adequate supportive care including hydration and oxygenation, the anion gap acidosis should improve. If, despite adequate supportive care, an anion gap metabolic acidosis worsens in a poisoned patient, the clinician should consider toxins that either form acidic metabolites (ethylene glycol, ibuprofen, methanol) or cause lactic acidosis by attenuating aerobic energy production (iron, cyanide).

**Box 1.3:** Agents increasing anionic gap

| |
|---|
| **M**ethanol, metformin, massive overdoses |
| **E**thylene glycol |
| **T**oluene |
| **A**lcoholic ketoacidosis |
| **L**actic acidosis |
| **A**cetaminophen (large overdoses) |
| **C**yanide, carbon monoxide, colchicine |
| **I**soniazid, iron, ibuprofen |
| **D**iabetic ketoacidosis |
| **G**eneralized seizure-producing toxins |
| **A**cetylsalicylic acid or other salicylates |
| **P**araldehyde, phenformin |

When a patient presents with an unexplained metabolic acidosis, a serum osmolality should be measured and the osmolal gap calculated. When an elevated osmolal gap is accompanied by anion gap acidosis, immediate consideration should be given to poisoning by methanol, ethylene glycol, and other less common toxic alcohols. The difference between the measured (OsmM) and calculated (OsmC) (Equation 2) is the osmol gap (OG): OG = OsmM - OsmC. If a significant

osmol gap is discovered, the difference in the two values may represent the presence of foreign substances in the blood.

Equation 2: OsmC = 2[Na meq L] + [BUN (mmol/L)] + [Glucose (mmol/L)] + [ethanol (mmol/L)]

A list of possible causes of an elevated osmol gap is given in Table 1.2. Traditionally, a normal gap has been defined as ≤10 mOsm/kg. However, this value is affected by the time of measurement following ingestion of a toxicant. If the time is long, it is assumed that the toxicant could be metabolized to acid metabolites that do not have osmotic activity. Thus, the OG should be used with caution as an adjunct to clinical decision making and not as a primary determinant to rule out toxic alcohol ingestion.

**Table 1.2:** Toxicants causing elevated Osmol gap

| Toxic alcohols | Drugs/additives | Other chemicals |
|---|---|---|
| Ethanol | Isoniazid | Ethyl ether |
| Isopropanol | Mannitol | Acetone |
| Methanol | Propylene glycol | Trichloroethane |
| Ethylene glycol | Glycerol | |
| | Osmotic contrast dyes | |

Toxicological screens are usually ordered in a shotgun fashion and are fraught with significant test limitations: i) immunoassays cover few commonly abused drugs but not dangerous drugs and poisons; ii) have little clinical correlation if the specimen is collected too early or too late. Urine drug tests often detect drug metabolites and may remain positive for several days after the exposure. Blood or serum drug tests are generally positive for much shorter time periods, and iii) a routine urine test is associated with false-positive and false-negative results.

As much as possible qualitative panels should be used when the result is expected to alter patient management or disposition (such as color of urine; orange to red orange for lead, rifampicin, mercury; greenish blue for copper sulfate, methylene blue; pink for ampicillin, cephalosporins; brown for chloroquine, carbon tetrachloride). Quantitative blood tests should be ordered only for those drugs or toxins for which blood levels predict toxicity or guide specific therapy. Such drugs include acetaminophen (paracetamol), salicylates, theophylline, lithium, lead, iron, carbon

monoxide, methemoglobin, toxic alcohols, anticonvulsants, and digoxin. If the injested substance is unknown, a routine acetaminophen quantitative measurement is recommended.

### 1.4.5 Electrocardiogram

Electrocardiographic (ECG) changes in the poisoned patient are commonly encountered. Toxins can be placed into two broad classes based on their ECG effects (Table 1.3).

a. Those associated with the potential for QT prolongation: this drug induced QT prolongation may lead to polymorphic ventricular tachycardia, most often as torsades de pointes. QT prolongation is considered to occur when the QTc interval is greater than 440 ms in men and 460 ms in women. The potential for an arrhythmia for a given QT interval will vary depending on the specific drug.
b. The other group includes toxins that inhibit fast cardiac sodium channels and thereby prolong the QRS complex. The Na+ channel blockers can cause slowed intraventricular conduction, unidirectional block, the development of a re-entrant circuit, and a resulting ventricular tachycardia or ventricular fibrillation.

The recognition of specific ECG changes associated with other clinical data (toxidromes) can lead clinicians to specific therapies that can be potentially lifesaving. Therefore, all seriously poisoned patients, particularly exposure to one of the agents listed in Table 3 is suspected, should have a minimum of an initial ECG. Repeat ECGs and cardiac monitoring would also be indicated if an ECG abnormality is identified or if the patient is at risk for delayed toxicity.

**Table 1.3:** Toxins associated with electrocardiographic changes

| **Toxins that prolong QT interval** | **Toxins that prolong QRS complex** |
|---|---|
| Antihistamines (Diphenhydrammine, loratidine)<br>Antipsychotics (Chlorpromazine, Haloperidol, Resperidone)<br>Chloroquine, Clarithromycin, Erythromyicin, Methadone, Floroquionolnes, Pentamidine, Tacrolimus<br>Antiarrhythmics (Qunindine, Procainamide, Amiodarone), tricyclic antidepressants. | Carbamazepine, Chloroquine, Cocaine, Diltiazem, Diphenhydramine, Hydroxchloroquine, Phenothiazines, Propranolol, Quinine, Verapamil, Antiarrhythmics (Qunindine, Procainamide), tricyclic antidepressants |

### 1.4.6 Radiological studies

A plain abdominal radiograph can reveal radiopaque pills, drug filled packets, or other toxic material. Drugs or toxins that are likely to be visible on films can be recalled by the mnemonic COINS (Box 1.4).

**BOX 1.4:** The mnemonic COINS

| COINS |
| --- |
| • **C**hloral hydrate, Cocaine packets, Calcium<br>• **O**pium packets<br>• **I**ron; other heavy metals such as lead and mercury<br>• **N**euroleptic agents<br>• **S**ustained release or enteric coated agents |

Patients who have tachypnea, hypoxia, obtundation, or coma should have a chest radiograph performed to search for potential causes of hypoxemia: chemical or aspiration pneumonitis, cardiogenic or noncardiogenic pulmonary edema (acute lung injury), and atelectasis. Drugs that can cause noncardiogenic pulmonary edema can be remembered by the mnemonic MOPS.

- **M**eprobamate, methadone
- **O**pioids
- **P**henobarbital, Propoxyphene, Phosegene
- **S**alicylates

**Note:** If a patient is presented with altered mental status and the poisoning agent insufficiently explains his/her altered mental status, patiet may need CT (computed tomography) of the head or magnetic resonance imaging (MRI). If the patient has adtional fever, lubar puncture (LP) might be considered.

## 1.5 Management

**Genereal principles**

Patients with acute poisoning are a heterogeneous group. Management of an individual patient requires more than an understanding of the agent ingested. To formulate a rational management plan, the clinician must also consider the dose ingested, time since ingestion, clinical features, patient factors, geographical location, and available medical facilities. A highly organized

approach is essential if the emergency physician is to ensure effective delivery of time-critical interventions while at the same time devising a management plan tailored to the individual patient's needs in that particular medical setting.

The poisoned patient should be kept under close observation with frequent evaluations of the level of consciousness, oxygenation status, and vital signs. This observation is important, particularly with the patient who presents in a stable condition, because continued absorption of an ingested substance may lead to delayed clinical evidence of poisoning. An ECG and continuous cardiac monitoring are indicated for any agent with potential cardiac toxicity. An ECG should also be routinely obtained in patients who have polysubstance ingestion and in cases of unknown suicidal ingestions.

**Pregnancy**

In general, any condition that leads to a severe metabolic derangement in the pregnant woman is likely to have an adverse impact on the developing fetus. In general, close attention should be paid to Airway, oxygenation and hemodynamic stability in the management of pregnant women with poisoning.

Gastrointestinal decontamination is frequently a part of the early management of acute poisoning in the non-pregnant patient. Gastric lavage is not specifically contraindicated for the pregnant patient; the usual concerns about protecting the airway apply to the pregnant patient as well. There is no specific contraindication to the use of activated charcoal in a pregnant woman. There may be a specific role for whole-bowel irrigation in the management of several xenobiotic exposures, particularly in the treatment of iron overdose in pregnancy (see below). The use of polyethylene glycol is generally safe in pregnant women.

In considering the use of antidotes, the primary concern should be for the health of the pregnant woman. Almost all antidotes are designated as FDA pregnancy-risk category C (there is little specific information to guide their use). Ethanol is labeled as category D (positive evidence of risk), although this is presumably related to chronic use throughout pregnancy, not as an antidote. Fomepizole, which has replaced ethanol as the preferred antidote for toxic alcohol poisoning, is labeled as category C. N-acetyl cysteine, glucagon, and naloxone are category B medications

**Children**

Rapid triage is crucial, including airway, respiration, and circulation stabilization. Appropriate supportive or toxin-specific treatment should be initiated. Gastric decontamination, such as activated charcoal and gastric lavage, are no longer routinely recommended. These methods should be reserved for the most severe cases, with poison control center support. The use of ipecac is no longer recommended. A child with few symptoms or a witnessed toxin exposure may be monitored at home. However, some long-acting medications have delayed toxin effects and require additional surveillance.

### 1.5.1 Resuscitation

Assessment and management of immediate threats to the airway, breathing, and circulation in the acutely poisoned patient usually follow conventional lines (Box 1.5). Basic resuscitative measures, familiar to all emergency physicians will ensure survival of the vast majority of patients. In some specific situations, standard resuscitation algorithms may not apply. Examples of interventions specific to toxicology include sodium bicarbonate and hyperventilation to prevent or terminate ventricular tachycardia secondary to cyclic antidepressants and benzodiazepines to treat tachycardia secondary to sympathomimetic agents. Seizures, hypoglycemia, and hyperthermia must be detected and treated promptly to ensure good neurological outcome. Toxin-induced seizures tend to be global central nervous system (CNS) processes as opposed to focal processes like those seen in patients who have epilepsy or CNS structural lesions. Toxic seizures are usually controlled with iv benzodiazepines. Barbiturates are second line treatment. Pyridoxine is an additional option for seizures associated with poisoning from isoniazid. Phenytoin is contraindicated in the treatment of toxic seizures. Occasionally, administration of an antidote may constitute an essential component of initial resuscitation.

### 1.5.2 Risk assessment

Following resuscitation, risk assessment is the next essential step in management of the poisoned patient (Box 1.6). Risk assessment is a distinct cognitive process through which the clinician attempts to predict the likely clinical course and potential complications for the individual patient at that particular presentation. Risk assessment should be quantitative and take into account agent, dose, time of ingestion, current clinical status and individual patient factors (for example, weight and comorbidities). Risk assessment is vital as it allows the clinician to make specific

decisions about all subsequent management steps (appropriate supportive care and monitoring; screening and specialized testing; decontamination; enhanced elimination; antidotes and disposition) that are appropriate to the individual patient at that particular time.

**Box 1.5: Management of anaphylaxis**

Anaphylaxis → Airway, Breathing, Circulation, Disability, Exposure

↓

Diagnosis (look for acute on set of illness, life threatening airway (hoarseness, swelling, stridor /breathing ((rapid breathing, cyanosis, wheeze, fatigue, $SpO_2$<92%) /circulatory problems (pale, clammy, low blood pressure, faintness, drowsy / coma, and skin changes)

↓

Call for help, allow patient to lie flat, raise patient's leg

↓

Adrenaline (give IM unless experienced with IV adrenaline): IM doses 1:1000 repeat after 5 min if no better; Adult and chidren >12 years, 500 μg (0.5 ml); Children 6-12 years, 300 μg (0.3 ml); < 6 years, 150 μg (0.15 ml); IV to be given by experienced specialists: Titrate: Adults 50 micrograms; Children 1 microgram/kg

↓

When skills and equipment available: establish airway, high flow oxygen, IV fluid challenge (adult, 500-1000 ml), Children, 20 ml/kg), Chlorpheniramine*, Hydrocortisone*. Monitor also pulse, ECG and Blood pressure

*Dose for cholrpheniramine and Hydrocortisone

| Patient group | Cholrpheniramine | Hydrocortisone |
|---|---|---|
| Adult or child > 12 years | 10 mg | 200 mg |
| Child 6 - 12 years | 5 mg | 100 mg |
| Child 6 months - 6 years | 2.5 mg | 50 mg |
| Child < 6 months | 250 micrograms/kg | 25 mg |

**Box 1.6:** Risk assessment

- Distinct cognitive step
- Quantitative
- Takes into account:
  - Agent(s)
  - Dose(s)
  - Time since ingestion
  - Current clinical status
  - Patient factors

### 1.5.3 Decontamination

Decontamination is required for toxic exposures affecting large dermal areas. Decontamination ideally occurs in a separate area adjacent to the ED, minimizing cross-contamination. Decontamination of severely poisoned patient must only be performed after careful consideration of the potential risks and benefits of the decontamination procedure. Although decontamination with various agents was once common practice, current recommendations reflect a trend towards more judicious use.

#### i. Skin decontamination

Corrosive agents rapidly injure the skin and must be removed immediately. In addition, many toxins are readily absorbed through the skin, and systemic absorption can be prevented only by rapid action. Be careful not to expose yourself or other care providers to potentially contaminating substances. Wear protective gear (gloves, gown, and goggles) and wash exposed areas promptly. In majority of the cases, health-care providers are not at significant personal risk for secondary contamination, and simple measures such as ED gowns and plain latex gloves are sufficient protection. Remove contaminated clothing and flush exposed areas with copious quantities of tepid (lukewarm) water or saline. Wash carefully behind ears, under nails, and in skin folds. Use soap and shampoo for oily substances.

#### ii. Ocular decontamination

Eye exposures may require local anesthetic (e.g., 0.5% tetracaine) instillation and lid retractors to facilitate copious irrigation with crystalloid solution. Alkalis produce greater injury than acids due to deep tissue penetration via liquefaction so that prolonged irrigation (1 to 2 h) may be required. Ten minutes after irrigation (allowing equilibration of crystalloid and conjunctival sac pH), conjunctival sac pH is tested. Irrigation continues until pH is <7.4. Ophthalmologic consultation is indicated for all ocular alkali injuries.

#### iii. Gastrointestinal decontamination

Gastric decontamination is not a routine part of poisoned-patient management; there is minimal evidence demonstrating positive benefit, and there are associated complications. Gastric decontamination may be considered in individual patients after a three-question risk-benefit analysis: (i) is this exposure likely to cause significant toxicity?; (ii) is gastrointestinal decontamination likely to change clinical outcome?; and (iii) is it possible that gastrointestinal decontamination will cause more harm than good? Although gastrointestinal decontamination

with activated charcoal and whole bowel irrigation may be of benefit particularly in early acute poisonings, it should only be attempted with careful consideration of the risks.

**a. Ipecac syrup** (inducing vomiting is no more recommended).

**b. Gastric lavage**

- Is the process of irrigating the gastric cavity to remove recently ingested material

**Indication:**

- It is rarely indicated. Not recommended for routine use in the poisoned patient. Gastric lavage may be considered in cases of ingestion of a life-threatening amount of poison within the previous hour where institution of supportive care and antidotal therapy would not ensure full recovery once absorbed. In certain circumstances, such as delayed gastric emptying accompanying intoxication with anticholinergic drugs and phenobarbitone, benefit may be noted longer after ingestion.

**Procedure:**

  - Ensure a protected airway if consciousness level is reduced.
  - Use a 36 to 40F-gauge orogastric tube (22 to 24F in children).
  - Position the patient on the left side with the head down 20 degrees.
  - Pass lubricated tube down the esophagus, a distance equal to that between chin and xiphoid process.
  - Confirm tube position by insufflation of air.
  - Gently lavage with 200 mL (10 mL/kg in children) of warm tap water.
  - Continue until returned fluid is clear.
  - Consider administration of activated charcoal via orogastric tube before removal.
- Liquid agents can be lavaged with a smaller diameter nasogastric tube, but extraction of pill fragments requires use of a largebore tube (36–40 F).
- Large bore tubing may only be placed via the orogastric route to avoid trauma to the nasopharynx.

**Complications:**

- Placement of an orogastric tube is a distressing procedure to perform in an awake patient and may be complicated by gagging and aspiration.
- Other serious complications such as laryngospasm, dysrhythmia and perforation.
- Aspiration pneumonia/hypoxia

- Water intoxication
- Hypothermia
- Time consuming, resulting in delay instituting other definitive care

**Contraindication:**

- Contraindicated in cases of acid, alkali or hydrocarbon ingestion, and in unawaked and absence of gag reflex because of the risk of aspiration.
- Supportive care/antidote likely to lead to recovery
- Unstable, requiring further resuscitation (hypotension, seizures)

**c. Activated charcoal**

**Indications:**

- Activated charcoal minimizes absorption of drugs by adsorbing them onto its surface.
- Charcoal administration has become the decontamination strategy of choice to prevent poisoning after toxicant ingestion and is most effective when used in the 1$^{st}$ hour after ingestion.
- Possesses large surface area that when administered orally, adsorbs ingested xenobiotics within the gastrointestinal tract thereby preventing systemic absorption.
- Some agents such as metals, ions and alcohols do not bind to charcoal.
- Significant increase in clearance for a number of drugs when repeated doses of 0.5 to 1 g per kg of activated charcoal are given every 4 to 6 h.

**Contraindication:**

In patients with an unprotected airway (e.g., deeply comatous, depressed gag reflex) or a disrupted GI tract (e.g., after severe caustic ingestion, hypoactive bowel sound) or in patients in whom charcoal therapy may increase the risk and severity of aspiration (e.g., hydrocarbons). In addition, nontoxic ingestion, in this case toxin not adsorbed by activated charcoal and recovery will occur without administration of activate charcoal.

**Complications:** such as bowel perforation or obstruction following multidose charcoal administration, vomiting, aspiration of the activated charcoal and impaired absorption of orally administered antidotes.

**Dose and Administration:**

- Poisoning (reduction of absorption), Oral: as soon as possible after ingestion of poison, **Adult,** 50–100 g as a single dose; **Infant,** 1 g/kg as a, single dose; **Child** 1–12 years, 25 g as a single dose (50 g in severe Poisoning).
- Poisoning (active elimination or multiple dose), Oral: **Adult,** 50 g every 4 hours (in case of intolerance 25 g every 2 hours); **Infant,** 1 g/kg every 4–6 hours; **Child** Over 1 year, 25–50 g every 4–6 hours.

**d. Whole bowel irrigation**

**Indications:**

- It uses a laxative agent such as polyethylene glycol to fully flush the bowel of stool and unabsorbed xenobiotics.
- May be considered for substantial ingestions of iron, sustained release products, enteric coated products and symptomatic acute lead toxicity with known lead particles in the gastrointestinal tract. It has been used for other metal ingestions (e.g., lead), overdoses of sustained-release medications (e.g., lithium, theophylline), ingested pharmaceutical patches, and ingestions of vials or packages of illicit drugs. It might also be useful in particularly massive and/or late-presenting overdoses for which the efficacy of gastric emptying and/or charcoal is expected to be suboptimal. The technique may be used by mouth in cooperative patients or by NG tube; the usual recommended dosing is 500 mL per hour (25ml/kg/hr, maximum 2L/h) in children and 2 L per hour in adolescents and adults.

**Contraindication:**

- In ileus, bowel obstruction or perforation, and in patients with hemodynamic instability. Unprotected airway, hemorrhage, Intractable vomiting

**Complications:**

- Nausea, vomiting, Pulmonary aspiration, Time consuming; possible delay instituting other definitive care

### 1.5.4 Antidotes

Although most poisonings are managed primarily with appropriate supportive care, there are several specific antidote agents that may be employed. Table 1.4 lists some of the more common antidotes for specific poisonings.

**Table 1.4**: **Antidotes commonly used for toxins**

| S. No. | Antidote | Poisoning indication |
|---|---|---|
| 1. | Acetyl cysteine injection, 200 mg/ml in 10ml ampoule | Acetaminophen |
| 2. | Polyvalent Immune Fab, ovine (Snake Venom Antiserum polyvalent Injection, 10ml) | Snake bite of unknown snake type |
| 3. | Atropine Sulfate Injection, 1mg/ml in 1 ml ampoule | Organophosphorus and N-methyl Carbamates |
| 4. | Calcium chloride *Injection, 10% (100mg/ml)* | Fluoride, Calcium Channel blockers |
| 5. | Calcium gluconate *Injection, 10% in 10ml ampoule* | Fluoride, Calcium Channel blockers, Magnesium sulfate |
| 6. | Calcium disodium EDTA† | Lead |
| 7. | Calcium trisodiumpentetate (CaDTPA) | Plutonium, Americium or Curium |
| 8. | Cyanide Antidote Kit* or Hydroxicobalamine HCl | Cyanide |
| 9. | Deferoxamine mesylate | Iron |
| 10. | Digoxin Immune Fab (Ovine) Digoxin specific, antibody fragments Powder for injection, 40mg | Cardiac glycosides/ Steroids |
| 11. | Ethanol | Methanol or Ethylene glycol |
| 12. | Flumazenil* *Injection, 0.1 mg/ml in 5 ml ampoule* | Benzodiazepine |
| 13. | Glucagon HCl | B-blocker, Calcium channel blockers |
| 14. | Methylene blue | Methemoglobinemia |
| 15. | Naloxone HCl Injection, 0.02mg/ml in 2ml ampoule, 0.4mg/ml in 1ml and 10ml ampoule, 1mg/ml | Opioid and Clonidine |
| 16. | Octeriotide acetate | Sulphonylurea |
| 17. | Physostigmine salicylate Injection, 1mg/ml in 1ml and 2ml ampoule | Anticholinergic syndrome |
| 18. | Pralidoxime chloride Powder for injection, 1g/vial | Organophosphates and N-methyl Carbamate insecticides |
| 19. | Pyridoxine hydrochloride *Injection, 50mg/ml in 2ml ampoule, 150mg/ml* | INH, Hydrazine |
| 20. | Sodium bicarbonate Injection : | Sodium channel blockers;TCA |

| | | |
|---|---|---|
| 21. | Phytomenadione (Vitamin K inj.) | Warfarin, Rodent poisons |
| 22. | Protamine Sulphate Inj. | Heparin |
| 23. | Sodium Polystyrene Sulphonate Powder | Hyperkalemia |
| 24. | Dextrose 40% injection | Insulin, oral hypoglycemic agents |
| 25. | Thiamine | Alcohol intoxication |
| 26. | Trimethoprim, methotrexate, | Leucovorin(Folinic acid) |
| 27. | Caffeine | Propranolol |
| 28. | Penicillamine | Lead, copper, mercury, |
| 29. | Activated charcoal<br>*Tablet, 125mg, 250mg*<br>*Powder for reconstitution, 15gm/120ml, 25gm*<br>*Gel, 300ml* | |
| 30. | **Apomorphine Hydrochloride**<br>*Injection, 3 mg/ml in 1 ml ampoule* | Parkinsonism |

***** Contraindicated in some cases in chronic habitual BZD users, TCA overdoses as it precipitates seizure.

### 1.5.5 Enhanced elimination technique

In severely poisoned patient, enhancing the toxin elimination may improve outcomes for some poisonings.

i. **Urine alkalinization**:

**Indication:** it may be considered for agents that are excreted as weak acids in the urine (Moderate to severe salicylate toxicity not meeting criteria for hemodialysis). By alkalinizing the urine through use of iv sodium bicarbonate, these weak acids will remain in a more polar ionized form in the urine that limits reabsorption and enhances elimination. Urine alkalinization may be considered for, 2, 4-dichlorophenoxyacetic acid, methotrexate, phenobarbital and salicylates.

**Contraindications**: Preexisting fluid overload, renal impairment, and uncorrected hypokalemia.

**Complications:** Hypokalemia, volume overload, alkalemia and Hypocalcemia (usually mild)

ii. **Dialysis:**

Dialysis is used to remove toxins or overdose of drugs and can be hemodialysis or hemoperfusion.

**Hemodialysis**

Hemodialysis is movement of solute down a concentration gradient across a semipermeable membrane.

**Indications:** it may be considered for poisons that are amenable to filtration across dialysis membranes. These include agents that possess low volume of distribution (Vd), low protein binding, low endogenous clearance, low molecular weight. Examples of agents that are commonly encountered and may require hemodialysis include Lithium, Metformin lactic acidosis, Phenobarbital, Salicylates, Valproic acid, Methanol/ethylene glycol, Metformin-induced lactic

**Contraindication:** Hemodynamic instability, Infants (generally), Poor vascular access and Significant coagulopathy.

**Hemoperfusion**

Hemoperfusion is movement of toxin from blood, plasma, or plasma proteins onto a bed of activated charcoal (or other adsorbents).

**Indications:** it is useful for toxins with low Vd, low endogenous clearance, and bound by activated charcoal. Examples of agents are Theophylline (high-flux hemodialysis is an alternative), Carbamazepine (multidose activated charcoal or high-efficiency hemodialysis also effective) and Paraquat (theoretical benefit only if instituted early after exposure).

**Contraindication:** Hemodynamic instability, Infants (generally), Poor vascular access, Significant coagulopathy and toxin not bound to activated charcoal.

### 1.5.6 Disposition

An initial risk assessment allows early planning for appropriate disposition. Arrangements should be made for a patient to be admitted to an environment capable of providing an appropriate level of monitoring and supportive care (and occasionally specific antidotal or enhanced elimination therapies) until the effects of poisoning resolve. These conditions can usually be met at the initial institution but if not, transfer to an institution with these capabilities must be made. Importantly, with acute poisoning, transfer may take place during the most severe phase of the illness or even during the period where the patient's clinical status is likely to deteriorate. For these reasons, the patient must be stabilized as far as possible prior to transport, and transfer should not involve an interval of a lower level of supportive care and monitoring.

Management should be discussed with the accepting institution, to allow mobilization of resources and preparation for urgent interventions.

**Note:** In all cases, patients who have deliberately self-poisoned and who have suicidal ideation require appropriate mental health assessment before disposition and discharge. All acts of deliberate self harm must be taken extremely serious. This assessment and disposition planning begins before the clinical resolution of the effects of acute poisoning.

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# Chapter 2: Specific poisons and drugs: diagnosis and treatment

## ACETAMINOPHEN/PARACETAMOL

Acetaminophen (Panadol®, Tylenol®, and other brand names) is a widely used drug found in many over-the-counter and prescription analgesics and cold remedies. When it is combined with another drug such as codeine, the more dramatic acute symptoms caused by the other drug may mask the mild and non-specific symptoms of early acetaminophen toxicity, resulting in missed diagnosis or delayed antidotal treatment.

**Toxicodynamics and toxicokinetics**

- **Hepatic injury.** One of the minor products (N-acetyl p-benzoquinone imine) of normal metabolism of acetaminophen by the cytochrome P-450 mixed-function oxidase system is highly toxic. Normally this reactive metabolite is rapidly detoxified by glutathione in liver cells. However, in an overdose, production of the toxic metabolite exceeds glutathione capacity and the metabolite reacts directly with hepatic macromolecules, causing liver injury.
- **Renal damage** may occur by the same mechanism, owing to renal metabolism.
- Overdose during **pregnancy** has been associated with fetal death and spontaneous abortion.
- **Pharmacokinetics.** Rapidly absorbed, with peak levels usually reached within 30–120 min (***Note:*** absorption may be delayed after ingestion of sustained-release products or with co-ingestion of opioids or anticholinergics). Vd = 0.8–1 L/kg. Eliminated by liver conjugation (90%) to glucuronides or sulfates; cytochrome P-450 mixed-function oxidase accounts for only about 3–8% but produces a toxic intermediate (see A, above). The elimination half-life is 1–3 h after therapeutic dose and maybe greater than 12 h after overdose.

**Toxic dose**

- **Acute ingestion** of more than 150–200 mg/kg in children or 6–7 g in adults' is potentially hepatotoxic.
  - Children younger than 10–12 years of age appear to be less susceptible to hepatotoxicity because of the smaller contribution of cytochrome P-450 to acetaminophen metabolism.

- On the other hand, the margin of safety is lower in patients with induced cytochrome P-450 microsomal enzymes, because more of the toxic metabolite may be produced.
- **High-risk patients** include alcoholics' and patients taking anticonvulsant medications or isoniazid. Fasting and malnutrition also increase the risk of hepatotoxicity, presumably by lowering cellular glutathione stores.

- **Chronic toxicity** has been reported after daily consumption of high therapeutic doses (4–6 g/day) by alcoholic patients. Children have developed toxicity after receiving as little as 60–150 mg/kg/day for 2–8 days.

**Clinical presentation**

Clinical manifestations depend on the time after ingestion.

- **Early:** after acute acetaminophen overdose, there are usually no symptoms other than anorexia, nausea, or vomiting. Rarely, a massive overdose may cause altered mental status and metabolic acidosis.
- **After 24–48 h,** when transaminase levels (AST and ALT) rise, hepaticnecrosis becomes evident. If acute fulminant hepatic failure occurs, encephalopathy and death may ensue. Encephalopathy, metabolic acidosis, and a continuing rise in the prothrombin time (PT) indicate poor prognosis. Acute renal failure occasionally occurs, with or without concomitant liver failure.
- **Diagnosis.** Prompt diagnosis is possible only if the ingestion is suspected and a serum acetaminophen level is obtained. However, patients may fail to provide history of acetaminophen ingestion, because they are unable (e.g., comatose from another ingestion), unwilling, or unaware of its importance. Therefore, if it is available, order acetaminophen levels in all overdose patients, regardless of the history of substances ingested. Interpretation is based on Rumack-Matthew nomogram (Figure 2.1) for single ingestion but not repeatitive or chronic ingestion. The nomogram only directly applies to an acetaminophen concentration obtained after a single oral exposure and during the window between 4 and 24 h post-ingestion. Hence, use of n-acetylcystiene (NAC) is guided by serum concentration after single ingestion. The nomogram line separating possible toxicity from unlikely toxicity is based on a 4-h acetaminophen concentration of 150 micrograms/mL (1000 micromoles/L) to increase the safety margin for treatment decisions.

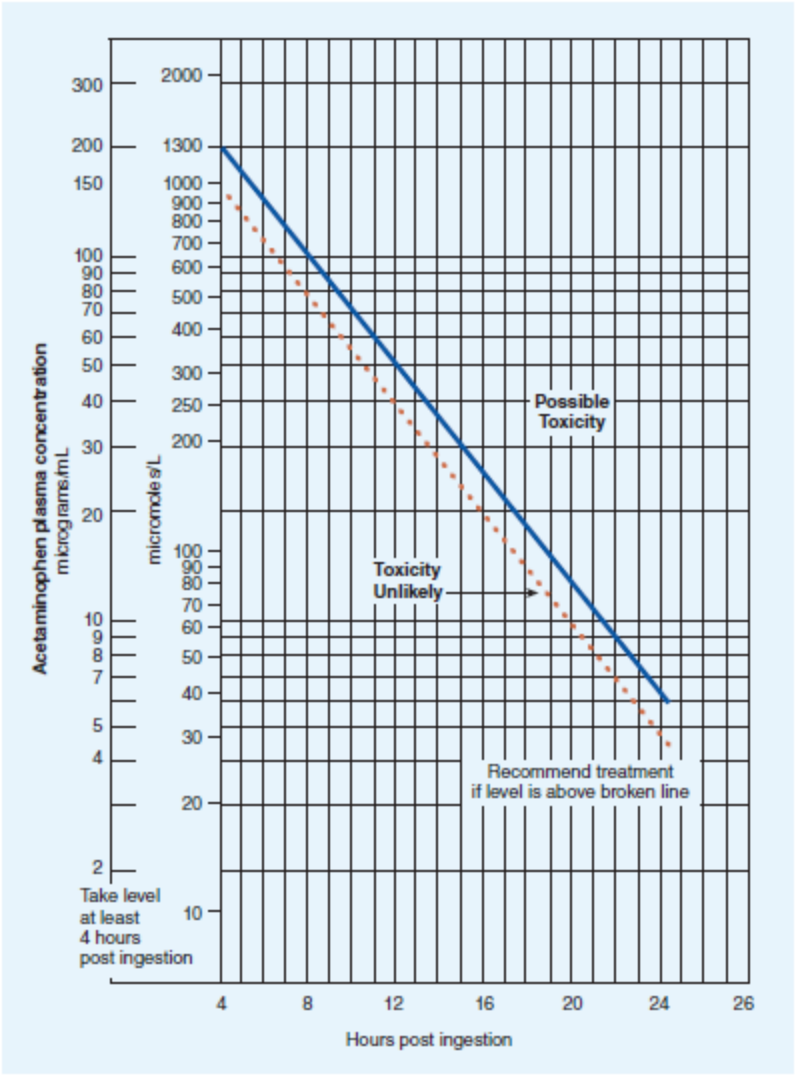


**Figure 2.1**: Rumack-Matthew nomogram: **a serum acetaminophen (**APAP) level 4 hours post ingestion > 150 mg/L shows possible toxicity

- **Specific levels.** After an **acute overdose,** obtain a 4-h-post-ingestion acetaminophen level to predict the likelihood of toxicity.
- **Other useful laboratory studies** include electrolytes, glucose, BUN, creatinine (the renal injury manisfested after 2-3 days), liver transaminases, and PT, INR, ECG (to exclude the prescence of coingested cardiotoxic substances). Abdominal ultrasound that may reveal hepatic enlargement and renal abnormality and inflamatory changes. Human chorionic gonadotrophin (hcg) because acetaminophen cross placent by 14 weeks. So antidote should be considered in pregnancy as soon as possible. CT for patients with altered mental status to see cerebral edema and encephalopathy.

**Treatment**

- **Emergency and supportive measures**
  - **Spontaneous vomiting** may delay the administration of antidote and charcoal (see below) and should be treated with metoclopramide or ondansetron.
  - Provide general supportive care for hepatic or renal failure if it occurs.Encephalopathy, metabolic acidosis, hypoglycemia, and progressiverise in the prothrombin time are indications of severe liver injury. Emergency **liver transplant** may be necessary for fulminant hepatic failure if available.
- **Specific drugs and antidotes.** If stat serum levels are not immediately available, initiate antidotal therapy with **NAC**, with a loading dose of 140 mg/kg orally followed by 70 mg/kg every 4 h for 17 more doses over 72 h. The effectiveness of NAC depends on **early treatment,** before the metabolite accumulates; it is of maximal benefit if started within 8–10 h and of diminishing value after12–16 h (however, treatment should not be withheld, even if as late as 48 h). If the patient vomits repeat the dose. If vomiting interferes with oral acetylcysteine administration, give it by gastric tube and use high-dose metoclopramide (1–2 mg/kg iv) or ondansetron, or give the NAC iv if necessary. IV NAC is recommended if there is altered mental status, sever vomiting. Mostly oral NAC has bad odor and unpleasant test.

Continuous IV infusion is recommended for acute ingestion, as follows:

- Loading dose: 150 mg/kg IV; mix in 200 mL of 5% dextrose in water (D5W) and infuse over 1 h
- Dose 2: 50 mg/kg IV in 500 mL D5W over 4 h
- Dose 3: 100 mg/kg IV in 1000 mL D5W over 16 h

Intermittent iv infusion may be considered for late-presenting or chronic ingestion. A loading dose of 140 mg/kg iv (diluted in 500 mL D5W) is infused over 1 h. Maintenance doses of 70 mg/kg IV are given every 4 hours for at least 12 doses (dilute each dose in 250 mL of D5W and infuse over a minimum of 1 hour).

**Note:** if we are giving activated charcoal, it should be give before po NAC. This is because activated charcoal will adsorb the po NAC.

- **For patients less than 20 kg:** consider giving NAC if the patient is at increased risk for toxicity, e.g., the patient is alcoholic, malnourished or fasting, or taking drugs that induce P-450 activity (e.g., anticonvulsants, INH); multiple or subacute overdoses; or time of ingestionis uncertain or unreliable.
- ***Note:*** after ingestion of **Extended Relief** tablets (Tylenol), which are designedfor prolonged absorption, there may be a delay before the peak acetaminophen level is reached. This can also occur after co-ingestion ofdrugs that delay gastric emptying, such as opioids or anticholinergics. Insuch circumstances, repeat the serum acetaminophen level at 8 hours andpossibly 12 hours.
- **Duration of NAC treatment.** 17 doses of oral NAC given over approximately 72 h. IV NAC for only 20 h. Then, if the serum acetaminophen level is below the limits of detection and liver transaminase levels are normal, NAC can be stopped. If there is evidence of hepatic toxicity, then NAC should be continued until liver function tests are improving.
- **Chronic** acetaminophen ingestions: patients may give a history of several doses taken over 24 h or more. In such cases, NAC treatment is advised if the amount ingested was more than 150–200 mg/kg or 6–7 g within a 24-hour period or if liver enzymes are elevated, or if the patient falls within a high-risk group (see above). Treatment may be stopped 36 h after the last dose of acetaminophen if the liver enzymes are normal.

- **Decontamination**
  - **Prehospital.** Administer activated charcoal, if available. Ipecac-inducedvomiting may be useful for initial treatment of children at home if it can begiven within 30 min of exposure.
  - **Hospital.** Administer activated charcoal. Although activated charcoal adsorbs some of the orally administered antidote NAC, this effect is not considered clinically important. Gastric emptying is not necessary if charcoal can be given promptly. Do not administer charcoal if more than3–4 h have passed since ingestion, unless delayed absorption is suspected (e.g., as with Tylenol Extended Relief or co-ingestants containingopioids or anticholinergic agents).
- **Enhanced elimination.** Hemoperfusion effectively removes acetaminophen from the blood but is not generally indicated because antidotal therapy is so effective.

## ANTIMICROBIALS

In general, harmful effects have resulted from allergic reactions or inadvertent iv overdose. Serious toxicity from a single acute ingestion is rare. Table 2.1 lists common antibiotics and their toxicities.

- **Mechanism of toxicity.** The precise mechanisms underlying toxic effects vary depending on the agent and are not well understood. In some cases, toxicity is caused by an extension of pharmacologic effects, while in other cases allergic or idiosyncratic reactions are responsible.
- **Toxic dose.** The toxic dose is highly variable, depending on the agent. Life threatening allergic reactions may occur after sub-therapeutic doses in hypersensitive individuals.
- **Clinical presentation.** After acute oral overdose, most agents cause only nausea, vomiting, and diarrhea. Specific features of toxicity are described in Table 2.1.
- **Diagnosis** is usually based on the history of exposure.
  - **Specific levels.** Serum levels for most commonly used antibiotics are usually available. Levels are particularly useful for predicting toxic effects of **aminoglycosides**, **chloramphenicol**, and **vancomycin.**

**Table 2.1: common antimicrobials and their toxicities**

| Drug | Half-Life* | Toxic Dose or Serum Level | Toxicity |
|---|---|---|---|
| Acyclovir | | Chronic | High-dose chronic therapy has caused crystalluria and renal failure. Acute overdose not likely to cause symptoms. |
| Aminoglycosides<br>Gentamicin<br>Neomycin<br>Streptomycin | <br>2 h<br><br>2.5 h | <br>> 12 mg/L<br>0.5–1 g/d<br>> 40–50 mg/L | Ototoxicity to vestibular and cochlear cells; nephrotoxicity causing proximal tubular damage and acute tubular necrosis; competitive neuromuscular blockade if given rapidly iv with other neuromuscular blocking drugs. |
| Cephalosporins<br>Ceftriaxone | 4.3–4.6 h (bile) | Intravenous bolus over < 3–5 min | Pseudolithiasis (“gall-bladder sludge”). Shouldbe administered iv over 30 min |
| Chloramphenicol | 4 h | > 50 mg/L | Leukopenia, reticulocytopenia; circulatory collapse (gray baby syndrome). |
| Dapsone | 10–50 h | As little as 100 mg in an 18 month-old | Methemoglobinemia, sulfhemoglobinemia, hemolysis; metabolic acidosis; hallucinations, confusion; hepatitis. |
| Erythromycin | 1.4 h | Unknown | Abdominal pain; idiosyncratic hepatotoxicity |
| Isoniazid (INH) | 0.5–4 h | 1–2 g orally | Convulsions, metabolic acidosis; hepatotoxicity with chronic use. |

| | | | |
|---|---|---|---|
| Clindamycin | 2.4–3 h | Unknown | Hypotension and cardiopulmonary arrest afterrapid iv administration. |
| Metronidazole | 8.5 h | 5 g/d | Convulsions; at therapeutic doses may cause disulfiramlikeinteraction with ethanol |
| Penicillins (such as crystalline) | 30 min | 10 million units/ d IV, or CSF > 5 mg/L | Seizures with single high dose or chronic excessive doses in patients with renal dysfunction. |
| Ampicillin,<br>Amoxicillin | 1.5 h<br>1.3 h | Unknown | Acute renal failure caused by crystal deposition. |
| Rifampin | 1.7 h | 100 mg/kg/d | Facial edema, pruritus; headache, vomiting, diarrhea; red urine and tears. |
| Tetracyclines | 6–12 h | > 1g/d in infants<br>> 4 g/d in pregnancy<br>or > 15 mg/L | Benign intracranial hypertension.<br>Acute fatty liver. |
| Sulfonamides | | Unknown | Acute renal failure caused by crystal deposition. |
| Trimethoprim | 8–11 h | Unknown | Bone marrow depression; methemoglobinemia; hyperkalemia |
| Vancomycin | 4–6 h | > 80 mg/L | Ototoxic and nephrotoxic. Hypertension, skinrash/flushing (“red-man syndrome”) associatedwith IV administration. |
| Zidovudine (AZT) | 1.0 h | Unknown | Seizures (36 g overdose), bone marrow suppression (20 g overdose). |

*****Normal renal function

- **Other useful laboratory studies:** include complete blood count (CBC), electrolytes, glucose, BUN and creatinine, liver function tests, urinalysis, and methemoglobin level (for patients with dapsone overdose).

- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary.
  - ✓ Treat coma, seizures, hypotension, anaphylaxis, and hemolysis (See Rhabdomyolysis) if they occur.
  - ✓ Replace fluid losses resulting from gastroenteritis with intravenous crystalloids.
  - ✓ Maintain steady urine flow with fluids to alleviate crystalluria from overdosesof sulfonamides, ampicillin and amoxicillin.
  - **Specific drugs and antidotes**

- ✓ **Trimethoprim** poisoning: administer **leucovorin** (folinic acid). Folic acid is not effective.
- ✓ **Dapsone** overdose: administer **methylene blue** for symptomaticmethemoglobinemia.

➢ **Decontamination**

- ✓ **Prehospital.** Administer activated charcoal, if available.
- ✓ **Hospital.** Administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly.

➢ **Enhanced elimination.** Most antibiotics are excreted unchanged in the urine, so maintenance of adequate urine flow is important. The role of forced diuresis is unclear. Hemodialysis is not usually indicated, except in patients with renal dysfunction and a high level of a toxic agent.

- ✓ Charcoal hemoperfusion effectively removes **chloramphenicol** and is indicated after a severe overdose with a high serum level and metabolic acidosis.
- ✓ **Dapsone** undergoes enterohepatic recirculation and is more rapidly eliminated with repeat-dose activated charcoal.

## ANTICHOLINERGICS

Anticholinergic intoxication can occur with a wide variety of prescription and over-the counter medications and numerous plants, including mushrooms. Common drugs that possess anticholinergic activity include antihistamines, antipsychotics, antispasmodics, skeletal muscle relaxants, and tricyclic antidepressants.

- **Mechanism of toxicity: a**nticholinergic agents competitively antagonize the effects of acetylcholine at peripheral and central cholinoceptors. Exocrine glands, such as those responsible for sweating and salivation, and smooth muscle are mostly affected. The inhibition of muscarinic activity in the heart leads to rapid heart beat. Tertiary amines such as atropine have access to the brain.
- **Pharmacokinetics:** absorption may be delayed because of the pharmacologic effects of these drugs on gastrointestinal motility. The duration of toxic effects can be quite prolonged (eg, benztropine intoxication may persist for 2–3 days).

- **Toxic dose:** the range of toxicity is highly variable and unpredictable. Fatal atropine poisoning has occurred after instilling as little as 1–2 mg in the eye of a young child. Intramuscular (im) injection of 32 mg of atropine was fatal in an adult.
- **Clinical presentation:** the anticholinergic syndrome is characterized by warm, dry, flushed skin; dry mouth; mydriasis; delirium; tachycardia; paralytic ileus; and urinary retention. Jerky myoclonic movements and choreoathetosis are common. Hyperthermia, coma, and respiratory arrest may occur. Seizures are rare with pure antimuscarinic agents, although they may result from other pharmacologic properties of the drug (e.g., tricyclic antidepressants and antihistamines). In some patients, fever and altered mental status may mimick other diorders and patients may need a CT and some times LP to rule out meningitis.
- **Diagnosis:** is based on history of exposure and the presence of typical features such as dilated pupils and flushed skin. A trial dose of physostigmine (see below) can be used to confirm the presence of anticholinergic toxicity; rapid reversal of signs and symptoms is consistent with the diagnosis.
  - **Specific levels:** concentrations in body fluids are not generally available.Common over-the-counter agents are usually detectable on general urine toxicology screening.
  - **Other useful laboratory studies:** include electrolytes, glucose, arterial blood gases or pulse oximetry, and ECG monitoring.
- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if needed.
  - ✓ Treat hyperthermia, coma, and seizures if they occur.
  - **Specific drugs and antidotes:** if a pure anticholinergic poisoning is suspected, a small dose of **physostigmine** (0.5–1 mg iv in an adult, a maximum of 4 mg, can be given to patients with severe toxicity (e.g., hyperthermia, severe delirium, or tachycardia). ***Caution:*** physostigmine is capable of causing atrioventricular block, asystole, and seizures, especially in patients with tricyclic antidepressant overdoses. **Physostigmine can be used in cases of severe agitation and delirium from pure anticholinergic toxicity, especially in cases necessitating physical restraints and benzodiazepines resistance.** The adult dose of physostigmine is 0.5 to 2 mg (pediatric dose is 0.02 mg/kg with a maximum dose of 2 mg) by slow iv administration over 5 min. When effective, a

significant decrease in agitation may be apparent within 15 to 20 min. Provide continuous cardiac monitoring before and during administration of physostigmine to assess for potential bradycardia. 1st degree AV block and wide QRS are all contraindications. Monitor the patient for signs of cholinergic excess, such as diarrhea, urination, miosis, bradycardia, bronchospasm, bronchorrhea, emesis, lacrimation, and salivation. **In cases of uncertain anticholinergic poisoning, a diagnostic challenge with physostigmine is *not* recommended because of a small but increased risk of adverse effects in patients *without* anticholinergic toxicity.**

Physostigmine may be repeated in the same dose if required. Patients who remain asymptomatic for more than 6 h after the first dose of physostigmine will not require repeat physostigmine dosing. Contraindications to physostigmine use include asthma, nonpharmacologically mediated intestinal or bladder obstruction, cardiac conduction disturbances, and suspected concomitant sodium-channel antagonist poisoning.

- **Decontamination**
- ✓ **Prehospital.** Administer activated charcoal if available. Avoid ipecac syrup.
- ✓ **Hospital.** Administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly.
- **Enhanced elimination.** Hemodialysis, hemoperfusion, peritoneal dialysis, and repeat-dose charcoal are not effective in removing anticholinergic agents.

## ANTIDIABETIC AGENTS

All **insulin** products are given by the parenteral route, and all produce effects similar to that of endogenous insulin. They differ by antigenicity and by onset and duration of effect. Table 2.2 lists the various available antidiabetic agents. Other drugs/poisons and conditions can also cause hypoglycemia, including, among others, endocrine disorders (hypopituitarism, Addison'sdisease, myxedema), ethanol intoxication (especially pediatric), fasting, hepatic failure, propranolol intoxication, renal failure, salicylate intoxication, and valproic acid intoxication).

**Table II-2: Anti-diabetic Agents**

| Agent |
|---|
| Insulins<br>Isophane insulin (NPH)<br>Regular insulin |
| **Oral Sulfonylureas**<br>Glimepiride<br>Glipizide<br>Glyburide |
| **Other oral agents**<br>Metformin |

- **Mechanism of toxicity**
  - **Oral agents**
  - ✓ **Sulfonylureas:** lower blood glucose primarily by stimulating endogenous pancreatic insulin secretion and secondarily by enhancing peripheral insulin receptor sensitivity and reducing glycogenolysis.
  - ✓ **Biguanides:** metformin decreases hepatic glucose production and intestinalabsorption of glucose, while increasing peripheral glucose uptake and utilization. It does not stimulate insulin release, and is not likely to produce acute hypoglycemia. Severe **lactic acidosis** is a rare but potentially fatal side effect of metformin. It occurs mainly in patients with renal insufficiency, alcoholism, and advanced age, and has occurred after injection ofiodinated contrast agents resulted in acute renal failure. While metformin is not likely to cause hypoglycemia after acute overdose, it may contribute to the hypoglycemic effects of sulfonylureas or insulin (e.g., by limiting glucose uptake from the intestinal tract or decreasing hepatic glucose production).
  - **Insulin.** Blood glucose is lowered directly by stimulation of cellular uptake and metabolism of glucose. Cellular glucose uptake is accompanied by an intracellular shift of potassium and magnesium. Insulin also promotes glycogen formation and lipogenesis.
- **Toxic dose.**
  - **Sulfonylureas.** Toxicity depends on the agent and the total amount ingested.Toxicity may also occur owing to drug interactions, resulting in impaired eliminationof the oral agent.

- ✓ **Glyburide: a**cute overdose (10–15 mg) in a child produced profound hypoglycemic coma. In a 79 year old nondiabetic person, 5 mg caused hypoglycemic coma.
- ✓ **Interactions** with the following drugs may increase the risk of hypoglycemia: other hypoglycemics, sulfonamides, propranolol, salicylates, probenecid, pentamidine, valproic acid, dicumarol, cimetidine, MAO inhibitors, and alcohol. In addition, co-ingestion of alcohol may occasionallyproduce a disulfiram-like interaction.
- ✓ **Hepatic** or **renal insufficiency** may impair drug elimination and result in hypoglycemia.
- ➢ **Metformin.** Lactic acidosis occurred 9 hs after ingestion of 25 g of metformin by an 83-year-old patient.
- ➢ **Insulin.** Severe hypoglycemic coma and permanent neurologic sequelae have occurred after injections of 800–3200 units of insulin.

- **Clinical presentation.**
  - ➢ **Hypoglycemia:** may be delayed in onset depending on the agent used and the route of administration (i.e., sc vs. iv). Manifestations of hypoglycemia include agitation, confusion, coma, seizures, tachycardia, and diaphoresis. Serum potassium and magnesium levels may also be depressed. Note that in patients receiving beta-adrenergic blockers many of the manifestations of hypoglycemia (tachycardia, diaphoresis) may be blunted or absent.
  - ➢ **Lactic acidosis:** with metformin may begin with nonspecific symptoms such as malaise, vomiting, myalgias, and respiratory distress. The mortality rate for severe lactic acidosis is reportedly as high as 50%.
- **Diagnosis:** overdose involving a sulfonylurea or insulin should be suspected in any patient with hypoglycemia. Other causes of hypoglycemia that should be considered include alcohol ingestion (especially in children) and fulminant hepatic failure.
  - ➢ **Specific levels**
  - ✓ Serum concentrations of many agents can be determined in toxicology laboratories, but have little utility in acute clinical management.
  - ✓ Exogenously administered animal insulin can be distinguished from endogenous insulin (i.e., in a patient with hypoglycemia caused by insulinoma) by determination of C peptide (present with endogenous insulin secretion).

- **Other useful laboratory studies:** include glucose, electrolytes, magnesium, and ethanol. If metformin is suspected, obtain a venous blood lactate level.

- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary.
  - ✓ Treat coma and seizures if they occur.
  - **Specific drugs and antidotes**
  - ✓ Administer concentrated **glucose** as soon as possible after drawing a baseline blood sample for later blood glucose determination. In adults, give 50% dextrose (D50W), 1–2 mL/kg; in children, use 25% dextrose (D25W), 2–4 mL/kg.
  - ✓ Follow serum glucose levels closely for several hours after the last dose ofdextrose. Give repeated glucose boluses and administer 5–10% dextrose (D5–D10) as needed to maintain serum glucose level at or above 100mg/dL.
  - ✓ For patients with a **sulfonylurea overdose**, consider intravenous **octreotide** or **diazoxide,** if 5% dextrose infusions do not maintain satisfactory glucose concentrations.
  - ✓ Lactic acidosis may be treated with judicious doses of sodium bicarbonate. Excessive bicarbonate administration may worsen intracellular acidosis.
  - **Decontamination**
  - ✓ **Sulfonylureas: Prehospital:** administer activated charcoal if available. **Hospital:** administer activated charcoal. Gastric emptying is not necessary, if activated charcoal can be given promptly.
  - ✓ **Metformin:** because there is limited experience with the effects of acute overdoses of these agents, ingestion of a large or unknown amount should be treated with oral activated charcoal.
  - ✓ **Insulin:** orally ingested insulin is not absorbed and produces no toxicity, so gut decontamination is not necessary. Local excision of tissue at the site of massive intradermal injection has been performed, but the general utility of this procedure has not been established.
  - **Enhanced elimination**
  - ✓ **Sulfonylureas:** alkalinization of urine (pH 8 or greater) increases the renal elimination of chlorpropamide. Forced diuresis and dialysis procedures are of no known value for other

hypoglycemic agents. The high degree of protein binding of the sulfonylureas suggests that dialysis procedures would not generally be effective.

- ✓ **Metformin:** is effectively removed by hemodialysis, which can also help correct severe lactic acidosis.

## ANTIHISTAMINES

Antihistamines (H1 receptor antagonists) are commonly found in over-the-counter and prescription medications used for motion sickness, control of allergy-related itching, cough and cold palliation and as sleep aid (Table 2.3). Acute intoxication with antihistamines results in symptoms very similar to those of anticholinergic poisoning. H2 receptor blockers (cimetidine, ranitidine, and famotidine) inhibit gastric acid secretion but otherwise share no effects with H1 agents, do not produce significant intoxication, and are not discussed here.

- **Mechanism of toxicity:** H1 blockers are structurally related to histamine and antagonize the effects of histamine on H1 receptor sites. They possess anticholinergic effects (except the "non-sedating" agents: e.g.. loratadine). They may also stimulate or depress the CNS, and some agents (e.g., diphenhydramine) have local anesthetic and membrane-depressant effects in large doses.
- **Pharmacokinetics:** drug absorption may be delayed because of the pharmacologic effects of these agents on the gastrointestinal tract. Vd is generally large (3–20 L/kg). Elimination half-lives are highly variable, ranging from 1–4 h for diphenhydramine to 7–24 h for many of the others.
- **Toxic dose:** the estimated fatal oral dose of diphenhydramine is 20–40 mg/kg. In general, toxicity occurs after ingestion of 3–5 times the usual daily dose. Children are more sensitive to the toxic effects of antihistamines than adults.
- **Clinical presentation.**
  - ➢ An overdose results in many symptoms similar to anticholinergic poisoning: drowsiness, dilated pupils, flushed dry skin, fever, tachycardia, delirium, hallucinations, and myoclonic or choreoathetoid movements. Convulsions, rhabdomyolysis and hyperthermia may occur with a substantial overdose.
  - ➢ Massive **diphenhydramine** overdoses have been reported to cause QRS widening and myocardial depression similar to tricyclic antidepressant overdoses.

- **Diagnosis:** is generally based on the history of ingestion and can usually bereadily confirmed by the presence of typical anticholinergic syndrome. Comprehensive urine toxicology screening will detect most common antihistamines.
  - **Specific levels:** are not generally available or useful. Common over-the-counter antihistamines are usually detectable on general urine toxicology screening.
  - **Other useful laboratory studies:** include electrolytes, glucose, arterial blood gases or pulse oximetry and ECG monitoring (diphenhydramine).

**Table 2.3: Common H1 receptor antagonist antihistamines**

| **Class** | **Specific Drug** |
|---|---|
| **Ethanolamines** | Dimenhydrinate, Diphenhydramine |
| **Alkylamines** | Chlorpheniramine |
| **Piperazines** | Cetrizine, Meclizine |
| **Phenothiazines** | Promethazine |
| **Others,** Cyproheptadine | Loratadine |

- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary.
  - ✓ Treat coma, seizures, hyperthermia, and atypical ventriculartachycardia if they occur.
  - ✓ Monitor the patient for at least 6–8 h after ingestion.
  - **Specific drugs and antidotes:** there is no specific antidote for antihistamine overdose. As for anticholinergic poisoning, physostigmine has been used for treatment of severe delirium or tachycardia. **Sodium bicarbonate**, 1–2 meq/kg iv, may be useful for myocardial depression and QRS interval prolongation after a massive diphenhydramine overdose.
  - **Decontamination**
  - ✓ **Prehospital:** administer activated charcoal if available.
  - ✓ **Hospital.** Administer activated charcoal. Consider gastric lavage for massive ingestions.
  - **Enhanced elimination:** hemodialysis, hemoperfusion, peritoneal dialysis, and repeat-dose activated charcoal are not effective in removing antihistamines.

## BARBITURATES

Barbiturates are used as sedative-hypnotic agents, for induction of anesthesia, and for treatment of epilepsy and status epilepticus. They are often divided into four major groups by their pharmacologic activity and clinical use: ultrashortacting (Thiopental), short-acting, intermediate-acting, and long-acting (Phenobarbital).

- **Mechanism of toxicity:** all barbiturates cause generalized **depression of neuronal activity** in the brain. Interaction with a barbiturate receptor leads to enhanced ϒ-aminobutyric acid (GABA)-mediated chloride currents and results in synaptic inhibition. Hypotension that occurs with large doses is caused by depression of central sympathetic tone as well as by direct depression of cardiac contractility.
- **Pharmacokinetics** varies by agent and group.
  - **Ultrashort-acting** barbiturates are highly lipid-soluble and rapidly penetrate the brain to induce anesthesia, then are quickly redistributed to other tissues. For this reason, the clinical duration of effect is much shorter than the elimination half-life for these compounds.
  - **Long-acting barbiturates** are distributed more evenly and have long elimination half-lives, making them useful for once-daily dosing.
- **Toxic dose:** the toxic dose of barbiturates varies widely and depends on the drug, the route and rate of administration, and individual patient tolerance. In general, toxicity is likely when the dose exceeds 5–10 times the hypnotic dose. Chronic users or abusers may have striking tolerance to depressant effects.
  - The potentially fatal **oral dose** of shorter-acting agents is 2–3 g, compared with 6–10 g for phenobarbital.
  - Several deaths were reported in young women undergoing therapeutic abortion after they received rapid **intravenous injections** of as little as 1–3 mg/kg of methohexital.
- **Clinical presentation:** the onset of symptoms depends on the drug and the route of administration.
  - Lethargy, slurred speech, nystagmus, and ataxia are common with mild to moderate intoxication. With higher doses, hypotension, coma, and respiratory arrest commonly occur. With deep coma, the pupils are usually small or mid-position; the patient may lose all reflex activity and appear to be dead.

- **Hypothermia** is common in patients with deep coma, especially if the victim has suffered exposure to a cool environment. Hypotension and bradycardia commonly accompany hypothermia.

- **Diagnosis:** is usually based on history of ingestion and should be suspected in any epileptic patient with stupor or coma. Although skin bullae are sometimes seen with barbiturate overdose, these are not specific for barbiturates. Other causes of coma should also be considered.
  - **Specific levels** of phenobarbital: concentrations greater than 60–80 mg/L are usually associated with coma and those greater than 150–200 mg/L with severe hypotension. For short- and intermediate-acting barbiturates, coma is likely when the serum concentration exceeds 20–30 mg/L. Barbiturates are easily detected in routine urine toxicologic screening.
  - **Other useful laboratory studies:** include electrolytes, glucose, BUN, creatinine, arterial blood gases or pulse oximetry, and chest x-ray.
- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Protect the airway and assist ventilation if necessary.
  - ✓ Treat coma, hypothermia, and hypotension if they occur.
  - **Specific drugs and antidotes:** there is no specific antidote.
  - **Decontamination**
  - ✓ **Prehospital:** administer activated charcoal, if available.
  - ✓ **Hospital:** administer activated charcoal. Consider gastric lavage for massive ingestion.
  - **Enhanced elimination**
  - ✓ **Alkalinization** of urine increases the urinary elimination of phenobarbital but not other barbiturates. Its value in acute overdose is unproved, and it may potentially contribute to fluid overload and pulmonary edema.
  - ✓ **Repeat-dose activated charcoal** has been shown to decrease the halflife of phenobarbital, but it has not been shown to actually shorten the durationof coma.
  - ✓ **Hemoperfusion** or hemodialysis may be necessary for severely intoxicated patients not responding to supportive care (ie, with intractable hypotension).

## BENZODIAZEPINES

The drug class of benzodiazepines contains many compounds that vary widely in potency, duration of effect, presence or absence of active metabolites, and clinical use (Table 2.4). In general, death from benzodiazepine overdose is rare, unless thedrugs are combined with other CNS-depressant agents such as ethanol or barbiturates.

**Table 2.4: Benzodiazepines for oral use**

| Drug | Half life (h) | Active metabolite | Oral adult dose (mg) |
|---|---|---|---|
| Chlordiazepoxide | 5–30 | Yes | 5–50 |
| Clonazepam | 20–60 | Yes | 0.5–2 |
| Diazepam | 50–100a | Yes | 5–20 |

*a*, half-life of active metabolite, to which effects can be attributed.

- **Mechanism of toxicity:** benzodiazepines enhance action of the inhibitory neurotransmitter GABA. They also inhibit other neuronalsystems by poorly defined mechanisms. The result is generalized depression of spinal reflexes and the reticular activating system. This may cause coma and respiratory arrest. Respiratory arrest is more likely with newer short-acting triazolobenzodiazepines. Cardiopulmonary arrest has occurred after rapid injection of diazepam, possibly because of CNS-depressant effects or because of the toxic effects of the diluent propylene glycol.
- **Pharmacokinetics:** most agents are highly protein bound (90–100%).
- **Toxic dose:** in general, the toxic to therapeutic ratio for benzodiazepines is very high. For example, oral overdoses of diazepam have been reported in excess of 15–20 times of the therapeutic dose without serious depression of consciousness. On the other hand, respiratory arrest has been reported after ingestion of 5 mg of triazolam and after rapid iv injection of diazepam, midazolam, and many other benzodiazepines. Also, ingestion of another drug with CNS-depressant properties (e.g., ethanol, barbiturates, opioids, etc) will likely produce additive effects.
- **Clinical presentation:** onset of CNS depression may be observed within 30–120 min of ingestion, depending on the compound. Lethargy, slurred speech, ataxia, coma, and respiratory arrest may occur. Generally, patients' with benzodiazepine-induced coma have hyporeflexia and mid-position or small pupil. Hypothermia may occur. Serious complications

are more likely when newer short-acting agents are involved or when other depressant drugs have been ingested.

- **Diagnosis:** is usually based on the history of ingestion or recent injection. The differential diagnosis should include other sedative-hypnotic agents, antidepressants, antipsychotics, and narcotics. Coma and small pupil do not respond to naloxone but will reverse with administration of flumazenil (see below).
  - **Specific levels:** serum drug levels are often available from regional commercial toxicology laboratories but are rarely of value in emergency management. Urine and blood qualitative screening may provide rapid confirmation of exposure. Certain immunoassays may not detect newer benzodiazepines or those in low concentrations.
  - **Other useful laboratory studies:** include glucose, arterial blood gases, or pulse oximetry.
- **Treatment.**
  - **Emergency and supportive measures**
    - ✓ Protect the airway and assist ventilation if necessary.
    - ✓ Treat coma, hypotension, and hypothermia, if theyoccur. Hypotension usually responds promptly to supine position and intravenousfluids.
  - **Specific drugs and antidotes: Flumazenil** is a specific benzodiazepine receptor antagonist that can rapidly reverse coma. However, because benzodiazepine overdose by itself is rarely fatal; the role of flumazenil in routine management has yet to be established. It is administered iv with a starting dose of 0.1–0.2 mg, repeated as needed up to a total of no more than 3 mg. It has some important potential drawbacks: (i) it may induce seizures in patients with tricyclic antidepressant overdose; (ii) it may induce acute withdrawal, including seizures and autonomic instability, in patients who are addicted to benzodiazepines; and (iii) resedation is common when the drug wears off after 1–2 h and repeated dosing is usually required.
  - **Decontamination**
    - ✓ **Prehospital:** administer activated charcoal if available.
    - ✓ **Hospital:** administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly.

- **Enhanced elimination:** there is no role for diuresis, dialysis, or hemoperfusion. Repeat-dose charcoal has not been studied.

## CARBAMAZEPINE

Carbamazepine is a first-line drug for the treatment of temporal lobe epilepsies and a variety of other seizure disorders and has found expanded use for neurogenic pain and psychiatric illnesses.

- **Mechanism of toxicity:** most toxic manifestations appear to be related to its anticholinergic effects. In addition, presumably because its chemical structure is similar to that of the tricyclic antidepressant, imipramine, acute carbamazepine overdose can cause seizures and cardiac conduction disturbances (although this is rare).
- **Pharmacokinetics**: carbamazepine is slowly and erratically absorbed from the gastrointestinal tract, and peak levels may be delayed for 6–24 h, particularlyafter an overdose (continued absorption for up to 72 h has been reported). Vd is 1.4 L/kg, and up to 3 L/kg after overdose. Up to 28% of a dose is eliminated in the feces, and there is enterohepatic recycling. The parent drug is metabolized to its 10, 11-epoxide, which is as active as the parent compound. The normal elimination half-life is approximately 15–24 h for carbamazepine and 5–10 h for the epoxide.
- **Toxic dose:** acute ingestion of over 10 mg/kg may result in a blood level above the therapeutic range of 4–8 mg/L. The recommended maximum dose is 1600 mg/d in adults (30 mg/kg/d in children, to a maximum of 1 g). Death has occurred after adult ingestion of 6–60 g, but survival has been reported after 80-g ingestion. Life-threatening toxicity occurred after ingestion of 5.8–10 g in adults and 2 g (148 mg/kg) in a 23-month-old child.
- **Clinical presentation.**
  - Ataxia, nystagmus, ophthalmoplegia, dystonia, mydriasis, and sinus tachycardia are common with mild to moderate overdose. With more serious intoxication, myoclonus, seizures, hyperthermia, coma, and respiratory arrest may occur. Atrioventricular (AV) block and bradycardia have been reported. Because of its structural similarity to tricyclic antidepressants, carbamazepine may cause QRS and QT interval prolongation; however, in case reports of overdose, QRS widening rarely exceeds 100–120 ms and is usually transient.

- After an acute overdose, manifestations of intoxication may be delayed for several hours because of erratic absorption. Cyclic coma and rebound relapse of symptoms may be caused by continued absorption from a tablet mass as well as enterohepatic circulation of the drug.
- Chronic use has been associated with mild leukopenia and thrombocytopenia. Aplastic anemia is extremely rare. Hyponatremia occasionally occurs.

- **Diagnosis:** is based on history of exposure and clinical signs such as ataxia, stupor, and tachycardia, along with elevated serum levels.
  - **Specific levels:** obtain a stat serum carbamazepine level and repeat levels every 4–6 h to rule out delayed or prolonged absorption. Serum levels greater than 10 mg/L are associated with ataxia and nystagmus. Serious intoxication may occur with serum levels greater than 20 mg/L, although there is poor correlation between levels and severity of clinical effects. Serious cardiac toxicity has not been reported with levels less than 40 mg/L. Death occurred in a patient who had a peak concentration of 120 mg/L. The epoxide metabolite may be produced in high concentrations after overdose. It is nearly equipotent, and may cross-react with some carbamazepine immunoassays to a variable extent.
  - **Other useful laboratory studies:** include CBC, electrolytes, glucose, arterial blood gases or oximetry, and ECG monitoring.
- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary (see chapter 1). Administer supplemental oxygen.
  - ✓ Treat seizures (Chapter1), coma (Chapter1), and arrhythmias (Chapter 1) if they occur.
  - ✓ Asymptomatic patients should be observed for a minimum of 6 h after ingestion.
  - **Specific drugs and antidotes:** there is no specific antidote. Sodium bicarbonate is of unknown value for QRS prolongation. Physostigmine is ***not*** recommended for anticholinergic toxicity.
  - **Decontamination**
  - ✓ **Prehospital:** administer activated charcoal if available.

- ✓ **Hospital.** Administer activated charcoal. Gastric lavage is not necessary after small to moderate ingestions if activated charcoal can be given promptly. For massive ingestions, consider repeated doses of activated charcoal and possibly whole bowel irrigation (see Chapter1).
- ➢ **Enhanced elimination:** in contrast to tricyclic antidepressants, the Vd of carbamazepine is small, making it accessible to enhanced removalprocedures.
- ✓ **Repeat-dose activated charcoal** is effective and may increase clearanceby up to 50%. However, it may be difficult to perform safely in a patient with obtundation and ileus, and there is no demonstrated benefit on morbidity or mortality.
- ✓ **Charcoal hemoperfusion** is highly effective and may be indicated for severe intoxication (e.g., status epilepticus, cardiotoxicity, serum level > 60mg/L) unresponsive to standard treatment.
- ✓ Peritoneal dialysis and hemodialysis do not effectively remove carbamazepine.

## CARDIAC GLYCOSIDES

Cardiac glycosides are found in several plants. Cardiac glycosides are used therapeutically in tablet form as digoxin and digitoxin.

- **Mechanism of toxicity:** cardiac glycosides inhibit the function of the sodium/potassium-ATPase pump. Acute overdose results in hyperkalemia (with chronic intoxication, the serum potassium level is usually normal or low, owing to the concurrent diuretic therapy). Vagal tone is potentiated, and sinus and atrioventricular (AV) node conduction velocity is decreased. Automaticity in Purkinje fibers is increased.
- **Pharmacokinetics:** the bioavailability of digoxin ranges from 60–80% and the absorption of digitoxin is more than 90%. Vd of digoxin is very large (5–10 L/kg), whereas it is small for digitoxin (about 0.5 L/kg). Peak effects occur after a delay of 6–12 h. The elimination half-life of digoxin is 30–50 h and for digitoxin is 5–8 days (owing to enterohepatic recirculation).
- **Toxic dose:** acute ingestion of as little as 1 mg of digoxin in a child or 3 mg of digoxin in an adult can result in serum concentrations well above the therapeutic range. More than these amounts of digoxin and other cardiac glycosides may be found in just a few leaves of oleander or foxglove. Generally, children appear to be more resistant than adults to the cardiotoxic effects of cardiac glycosides.

- **Clinical presentation:** intoxication may occur after acute accidental or suicidal ingestion or with chronic therapy. Signs and symptoms depend on chronicityof the intoxication.
  - With **acute overdose** vomiting, hyperkalemia, sinus bradycardia, sinoatrial arrest, and second- or third-degree AV block are common. Ventricular tachycardia or fibrillation may occur.
  - With **chronic intoxication** visual disturbances, weakness, sinus bradycardia, atrial fibrillation with slowed ventricular response rate or junctional escape rhythm, and ventricular arrhythmias (ventricular bigeminy or trigeminy, ventricular tachycardia, bidirectional tachycardia, and ventricular fibrillation) are common. Accelerated junctional tachycardia and paroxysmal atrial tachycardia with block are frequently seen. Hypokalemia and hypomagnesemia from chronic diuretic use may be evident and appear to worsen the tachyarrhythmias.
- **Diagnosis:** is based on history of recent overdose or characteristic arrhythmias (e.g., bidirectional tachycardia and accelerated junctional rhythm) in a patient receiving chronic therapy. Hyperkalemia suggests acute ingestion but may also be seen with very severe chronic poisoning. Serum potassium levels higher than 5.5 meq/L are associated with severe poisoning.
  - **Specific levels:** stat serum digoxin or digitoxin levels are recommended, although they may not correlate accurately with severity of intoxication. This is especially true after acute ingestion, when the serum level is high for 6–12 h before tissue distribution is complete. After use of digitalis-specific antibodies, the radioimmunoassay digoxin level is falsely markedly elevated. Therapeutic levels of digoxin are 0.5–2 ng/mL; of digitoxin, 10–30 ng/mL.
  - **Other useful laboratory studies:** include electrolytes, BUN, creatinine, serum magnesium, and ECG monitoring.
- **Treatment**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary (see Chapter 1).
  - ✓ Monitor the patient closely for at least 12–24 h after significant ingestion because of delayed tissue distribution.

- ✓ Treat **hyperkalemia** (chapter 1), if greater than 5.5 meq/L, with sodium bicarbonate (Give 1–2 mEq/kg iv bolus over 1–2 min; repeat as needed to improve cardiotoxic manifestations), glucose (0.5 g/kg iv) with insulin (0.1 U/kg iv). Administer regular insulin 10 U iv along with 50 mL of 50% dextrose (children: 0.1 U/kg insulin with 2 mL/kg of 25% dextrose), or sodium polystyrene sulfonate (Kayexalate, 0.5 g/kg PO (0.3–0.6 g/kg PO) in 2 mL/kg 70% sorbitol, is effective but takes several hours.). Do ***not*** use calcium; it may worsen ventricular arrhythmias. Mild hyperkalemia may actually protect against tachyarrhythmias. In summary, hyperkalemia in acute digoxin poisoning indicates severe toxicity and digoxin-Fab should be given to reduce mortality.
- ✓ Treat **bradycardia** or **heart block:** atropine is usually the drug of choice in this circumstance. For adults, give 0.5–1 mg iv; for children, give 0.02 mg/kg iv up to a maximum of 0.5 mg and 1 mg in adolescents. Repeat as needed. Note that 3 mg is a fully vagolytic dose in adults. If response is not achieved at 3 mg, the patient is unlikely to benefit from further treatment unless bradycardia is caused by excessive cholinergic effects (e.g., carbamate or organophosphate overdose). A temporary pacemaker may be needed for persistent symptomatic bradycardia.
- ✓ **Ventricular tachyarrhythmias:** may respond to lidocaine. Administer 1–1.5 mg/kg (usual adult dose 50–100 mg; children, 1 mg/kg) iv bolus at a rate of 25–50 mg/min, followed by infusion of 1–4 mg/min (20–50 mcg/kg/min) to maintain serum concentrations of 1.5–5 mg/L. If significant ectopy persists after the initial bolus, repeat doses of 0.5 mg/kg iv can be given if needed at 10-min intervals (to a maximum 300 mg or 3 mg/kg total dose; children may be given repeat 1 mg/kg doses every 5–10 min to a maximum of 5 mg/kg). In patients with congestive heart failure or liver disease, use half the recommended maintenance infusion dose or phenytoin, a loading dose of 15–20 mg/kg iv slowly at a rate not to exceed 50 mg/min (or 1 mg/kg/min in children) or to correction of low potassium or magnesium. Avoid quinidine, procainamide, and bretylium.
- ➢ **Specific drugs and antidotes:** Fab fragments of **digoxin-specific antibodies** (Digibind) are indicated for **(acute)** significant poisoning (e.g., severe hyperkalemia **(potassium >6.0 mEq/L)** and symptomatic arrhythmias not responsive to drugs described above) **or chronic toxicity with any life-threatening dysrhythmia** and possibly for prophylactic

treatment in a massive oral overdose with high serum levels. Digibind rapidly binds to digoxin and, to a lesser extent, digitoxin and other cardiac glycosides. The inactive complex that is formed is rapidly excreted in the urine. A full neutralizing dose of digoxin-Fab is based on an estimation of the total-body load of digoxin, which can be calculated from either the dose ingested or a steady-state serum digoxin level. In an acute poisoning, each vial of digoxin-Fab reverses approximately 0.5 milligram of ingested digoxin. In hemodynamically stable patients, half the calculated full neutralizing dose is infused, and the other half is given if an adequate clinical response is not seen in 1 to 2 h. A total of 200 to 480 mg of digoxin-Fab (5 to 12 vials) is required to effectively treat severely digoxin-toxic patients. When the ingested dose is unknown and serum level is unavailable, 10 vials are recommended as initial treatment in life-threatening situations. Digoxin-Fab are administered iv through a 0.22-mm filter over 30 min, except in cardiac arrest, when the dose is given as an iv bolus.

- **Decontamination**

✓ **Prehospital:** administer activated charcoal, if available.

✓ **Hospital:** administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly.

- **Enhanced elimination**

✓ Because of its large Vd, **digoxin** is not effectively removed by dialysis or hemoperfusion. Repeat-dose activated charcoal may be useful in patients with severe renal insufficiency, in which clearance ofdigoxin is markedly diminished.

✓ **Digitoxin** has a small Vd and also undergoes extensive enterohepatic circulation, and its elimination can be markedly enhancedby repeat-dose charcoal.

## CHLOROQUINE AND OTHER AMINOQUINOLINES

Chloroquine and other aminoquinolines are used in the prophylaxis or treatment of malaria and other parasitic diseases. Chloroquine and hydroxychloroquine are also used in the treatment of rheumatoid arthritis. Drugs in this class include chloroquine phosphate, hydroxychloroquine sulfate, mefloquine and primaquine phosphate. Chloroquine overdose is common, especially in countries where malaria is prevalent, and the mortality rate is 10–30%.

- **Mechanism of toxicity.**

- **Chloroquine:** blocks the synthesis of DNA and RNA and also has some quinidine-like cardiotoxicity. Hydroxychloroquine has similar actions but is considerably less potent.
- **Primaquine:** is an oxidizing agent and can cause methemoglobinemia or hemolytic anemia (especially in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency).

- **Pharmacokinetics:** chloroquine and related drugs are highly tissue-bound (Vd = 150–250 L/kg) and are eliminated very slowly from the body. The terminal half-life of chloroquine is 2 months. Primaquine is extensively metabolized with a half-life of 3–8 h to an active metabolite that is eliminated much more slowly (half-life 22–30 h) and can accumulate with chronic dosing.
- **Toxic dose:** the therapeutic dose of chloroquine phosphate is 500 mg once a week for malaria prophylaxis or 2.5 g over 2 days for treatment of malaria. Death has been reported in children after doses as low as 300 mg; the lethal dose of chloroquine for an adult is estimated to be 30–50 mg/kg.
- **Clinical presentation**
  - **Mild to moderate chloroquine overdose:** results in dizziness, nausea and vomiting, abdominal pain, headache and visual disturbances (sometimes including irreversible blindness), auditory disturbances (sometimes leading to deafness), agitation, and neuromuscular excitability.
  - **Severe chloroquine overdose:** may cause convulsions, coma, shock, and respiratory or cardiac arrest. Quinidine-like cardiotoxicity may be seen, including sinoatrial arrest, depressed myocardial contractility, QRS or QT interval prolongation, heart block, and ventricular arrhythmias. Severe hypokalemia sometimes occurs and may contribute to arrhythmias.
  - **Primaquine:** intoxication commonly causes gastrointestinal upset and may also cause severe methemoglobinemia or hemolysis; chronic treatment can cause ototoxicity and retinopathy.
  - **Mefloquine:** in therapeutic use or overdose may cause dizziness, vertigo, hallucinations, psychosis, and seizures.
- **Diagnosis:** the findings of gastritis, visual disturbances, and neuromuscular excitability, especially if accompanied by hypotension, QRS or QT interval widening, or ventricular

arrhythmias, should suggest chloroquine overdose. Hemolysis or methemoglobinemia should suggest primaquine overdose.

- **Specific levels:** chloroquine levels can be measured in blood but are not generally available. Because chloroquine is concentrated intracellularly, whole blood measurements are fivefold higher than serum or plasma levels.
- ✓ Plasma (trough) concentrations of 10–20 ng/mL (0.01–0.02 mg/L) are effective in the treatment of various types of malaria.
- ✓ Cardiotoxicity may be seen with serum levels of 1 mg/L (1000 ng/mL); serum levels reported in fatal cases have ranged from 1–210 mg/L (average, 55 mg/L).
- **Other useful laboratory studies:** include electrolytes, glucose, BUN, creatinine, and ECG monitoring. With **primaquine,** also include CBC, free plasma hemoglobin, and methemoglobin.

- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary (see Chapter 1).
  - ✓ Treat seizures (Chapter 1), coma (Chapter 1), hypotension (Chapter 1), and methemoglobinemia if they occur.
  - ✓ Treat massive hemolysis with blood transfusions if needed, and prevent hemoglobin deposition in the kidney tubules by alkaline diuresis (as for rhabdomyolysis; see Chapter 1).
  - ✓ Continuously monitor the ECG for at least 6–8 hours.
  - **Specific drugs and antidotes**
  - ✓ Treat cardiotoxicity as for quinidine poisoning with **sodium bicarbonate** (see chapter 4), 1–2 meq/kg IV.
  - ✓ **Epinephrine (noradrenaline)** infusion may be useful in treating hypotension via combined vasoconstrictor and inotropic actions. According to a study, dosing recommendation is 0.25 µg/kg/min, with increments of 0.25 µg/kg/min until adequate blood pressure was obtained, along with administration of high-dose diazepam and mechanical ventilation.
  - ✓ High-dose **diazepam** (2 mg/kg iv, given over 30 min after endotracheal intubation and mechanical ventilation) has been reported to reduce mortality in animals and to

ameliorate cardiotoxicity in human chloroquine poisonings. The mechanism of protection is unknown.

- **Decontamination** (see chapter 1)
- ✓ **Hospital:** if the patient arrives shortly after an overdose and yet not manifesting symptoms, administer activated charcoal. Perform gastric lavage for significant ingestions (e.g., > 30–50 mg/kg). Gastric emptying is probably not necessary after small ingestions if activated charcoal can be given promptly.
- **Enhanced elimination:** because of extensive tissue distribution, enhanced removal procedures are ineffective.

## DEXTROMETHORPHAN

Dextromethorphan is a common antitussive agent found in many over-the-counter cough and cold preparations. Much ingestion occurs in children, but severe intoxication is rare. Dextromethorphan is often found in combination products containing antihistamines, decongestants, ethanol, or acetaminophen.

- **Mechanism of toxicity:** Dextromethorphan is the d-isomer of 3-methoxy-N-methylmorphinan, a synthetic analogue of codeine. (The l-isomer is the opioid analgesic levorphanol.) Although it has approximately equal antitussive efficacy as codeine, dextromethorphan has no apparent analgesic or addictive properties and produces relatively mild opioid effects in overdose.
  - Both dextromethorphan and its O-demethylated metabolite appear to antagonize *N*-methyl-D-aspartate (NMDA) glutamate receptors, which may explain anticonvulsant properties and protection against hypoxia-ischemia observed in animal models.
  - Dextromethorphan inhibits reuptake of serotonin, and may lead to the **serotonin syndrome** (chapter 1) in patients taking MAO inhibitors. Serotoninergic effects and, probably, NMDA glutatmate receptor inhibition, may explain the acute and chronic abuse potential of dextromethorphan.
  - Dextromethorphan hydrobromide can cause bromide poisoning.
- **Pharmacokinetics:** Dextromethorphan is well absorbed orally, and effects are often apparent within 15–30 min (peak 2.5 h). The Vd is approximately 5–6 L/kg. The duration of effect is normally 3–6 h. A genetic polymorphism exists for the debrisoquin hydroxylase enzyme

(P450-II-DC). Dextromethorphan is a high-affinity substrate for this enzyme. Rapid metabolizers have a plasma half-life of about 3–4 h, but in slow metabolizers (about 10% of the population) the half-life may exceed 24 h. Inaddition, dextromethorphan competitively inhibits CYP2D6-mediated metabolism, leading to many potential drug interactions.

- **Toxic dose:** the toxic dose is highly variable and depends largely on other ingredients in the ingested product. Symptoms usually occur when the amount of dextromethorphan ingested exceeds 10 mg/kg. The usual recommended adult dailydose of dextromethorphan is 60–120 mg/d; in children age 2–5 years, up to 30 mg/d.
- **Clinical presentation.**
  - **Mild intoxication:** produces clumsiness, ataxia, nystagmus, and restlessness.Visual and auditory hallucinations have been reported.
  - With **severe poisoning:** stupor, coma, and respiratory depression may occur, especially if alcohol has been co-ingested. The pupil may be constricted or dilated. A few cases of seizures have been reported after ingestions of morethan 20–30 mg/kg.
  - **Serotonin syndrome:** severe hyperthermia, muscle rigidity, and hypertension may occur with therapeutic doses in patients taking **MAO inhibitors.**
- **Diagnosis:** should be considered with ingestion of any over-the-counter cough suppressant, especially when there is nystagmus, ataxia, and lethargy. Because dextromethorphan is often combined with other ingredients (e.g., antihistamines, phenylpropanolamine, or acetaminophen), suspect mixed ingestion.
  - **Specific levels:** both gas chromatography (GC) and high-performance liquid chromatography (HPLC) assays exist for serum and urine analysis, but are not generally available, nor are they clinically useful. Despite its structural similarity to opioids, even twice therapeutic doses of dextromethorphan are not likely to produce a false-positive urine opioid Enzyme multiplied immunoassay technique (EMIT) screen. Dextromethorphan is readily detected by comprehensive urine toxicology screening.
  - **Other useful laboratory studies:** include electrolytes, glucose, and arterial blood gases (if respiratory depression is suspected). Blood ethanol and acetaminophen levels should be obtained if those drugs are contained in the ingested product.
- **Treatment.**

- **Emergency and supportive measures:** most patients with mild symptoms (i.e., restlessness, ataxia, or mild drowsiness) can be observed for 4–6 h and discharged if they are improving.
- ✓ Maintain an open airway and assist ventilation if needed (see chapter 1).
- ✓ Treat seizures (chapter 1) and coma (chapter 1) if they occur.
- **Specific drugs and antidotes:** although **naloxone** (see chapter 4) has been reported effective in doses of 0.06–0.4 mg, other cases have failed to respond to as much as 2.4 mg.
- **Decontamination**
- ✓ **Prehospital:** administer activated charcoal if available. Do ***not*** induce vomiting, because signs of intoxication can develop rapidly.
- ✓ **Hospital.** Administer activated charcoal. Gastric emptying is not necessaryif activated charcoal can be given promptly.
- **Enhanced elimination:** the Vd of dextromethorphan is very large, and there is no role for enhanced removal procedures.

## ETHANOL

Commercial beer, wine, and liquors contain various amounts of ethanol. Ethanol is also found in a variety of colognes, perfumes, after-shaves, mouthwashes, some rubbing alcohols, many food flavorings (e.g., vanilla, almond, and lemon extracts), pharmaceutical preparations (e.g., elixirs), and many other products. Ethanol is frequently ingested recreationally and is the most common co-ingestant with other drugs in suicide attempts. Ethanol may also serve as an antidote in the emergency treatment of methanol and ethylene glycol poisonings (see chapter 3).

- **Mechanism of toxicity.**
  - **CNS depression:** is the principal effect of acute ethanol intoxication. Ethanol has additive effects with other CNS depressants such as barbiturates, benzodiazepines, opioids, antidepressants, and antipsychotics.
  - **Hypoglycemia:** may be caused by impaired gluconeogenesis in patients with depleted glycogen stores (particularly small children and poorly nourished persons).
  - Ethanol intoxication and chronic alcoholism also predispose patients to trauma, exposure-induced hypothermia, injurious effects of alcohol on thegastrointestinal tract and nervous system, and a number of nutritional disorders and metabolic derangements.

- **Pharmacokinetics:** ethanol is readily absorbed (peak 30–120 min) and distributed into the body water (Vd 0.5–0.7 L/kg or about 50 liters in the average adult). Elimination is mainly by oxidation in the liver and follows zero-order kinetics. The average adult can metabolize about 7–10 g/h or about 12–25 mg/dL/h (this rate is highly variable dependingon the individual and the blood alcohol level).
- **Toxic dose:** generally, 0.7 g/kg pure ethanol (approximately 3–4 drinks) will produce a blood ethanol concentration of 100 mg/dL (0.1 g/dL), legally considered as intoxication in many states but the Ethiopian level is unknown.
  - A level of 100 mg/dL decreases reaction time and judgment and may be enough to inhibit gluconeogenesis and cause hypoglycemia in children and patients with liver disease, but by itself is not enough to cause coma.
  - The level sufficient to cause deep coma or respiratory depression is highly variable, depending on the individual's degree of tolerance to ethanol. Although levels above 300 mg/dL usually cause coma in novice drinkers, chronic alcoholics may be awake with levels of 500–600 mg/dL or higher.
- **Clinical presentation.**
  - **Acute intoxication**
  - ✓ With **mild** to moderate intoxication, patients exhibit euphoria, mild incoordination, ataxia, nystagmus, and impaired judgment and reflexes. Social inhibitions are loosened, and boisterous or aggressive behavior is common. Hypoglycemia may occur, especially in children and in persons with reduced hepatic glycogen stores.
  - ✓ With **deep intoxication**, coma, respiratory depression, and pulmonary aspiration may occur. In these patients, the pupils are usually small and the temperature, blood pressure, and pulse rate are often decreased. Rhabdomyolysis may result from prolonged immobilization on a hard floor.
  - **Chronic ethanol abuse** is associated with numerous complications:
  - ✓ **Hepatic toxicity:** includes fatty infiltration of the liver, alcoholic hepatitis, and cirrhosis. Liver scarring leads to portal hypertension, ascites, and bleeding from esophageal varices and hemorrhoids; hyponatremia fromfluid retention; and bacterial peritonitis. Production of clotting factors is impaired leading to prolonged PT. Hepatic metabolism ofdrugs and endogenous toxins is impaired and may contribute to hepatic encephalopathy.

- ✓ **Gastrointestinal** bleeding may result from alcohol-induced gastritis, esophagitis, and duodenitis. Other causes of massive bleeding include Mallory-Weiss tears of the esophagus and esophageal varices. Acute pancreatitis is a common cause of abdominal pain and vomiting.
- ✓ **Cardiac** disorders include various dysrhythmias associated with potassium and magnesium depletion and poor caloric intake ("Holiday heart") and cardiomyopathy, which has been associated with long-term alcohol use as well as with ingestion of cobalt (which was once used to stabilize beer).
- ✓ **Neurologic** toxicity includes cerebral atrophy, cerebellar degeneration, and peripheral stocking-glove sensory neuropathy. Nutritional disorders such as thiamine (Vitamin B-1) deficiency can cause Wernicke's encephalopathy or Korsakoff's syndrome.
- ✓ **Alcoholic ketoacidosis:** is characterized by anion gap metabolic acidosis and elevated levels of betahydroxybutyrate and, to a lesser extent, acetoacetate. The osmolar gap may also be elevated, causing this conditionto be mistaken for methanol or ethylene glycol poisoning.
- ✓ **Alcohol withdrawal:** sudden discontinuation after chronic high-level alcohol use often causes headache, tremulousness, anxiety, palpitations, and insomnia. Brief, generalized seizures may occur usually within 6–12 h. Sympathetic nervous system overactivity may progress to **delirium tremens**, a lifethreatening syndrome charcaterized by tacycardia, diaphoresis, hyperthermia, and delirium, which usually manifests 48–72 h after cessation of heavy alcohol use. The delirium tremens may cause significant morbidity and mortality if untreated.
- ✓ **Other problems:** ethanol abusers sometimes intentionally or accidentally ingest ethanol substitutes such as isopropyl alcohol, methanol, or ethylene glycol. In addition, ethanol may serve as the vehicle for swallowing large numbers of pills in a suicide attempt. Disulfiram (Antabuse) use can cause a serious acute reaction with ethanol.

- **Diagnosis:** it is usually simple and performed based on history of ingestion, the characteristic smell of fresh alcohol or the fetid odor of acetaldehyde and other metabolic products, and the presence of nystagmus, ataxia, and altered mental status. It is imperative to consider other etiologies that may accompany or mimic intoxication, such as hypoglycemia, head trauma, hypothermia, meningitis, or intoxication with other drugs or poisons.

- **Specific levels:** serum ethanol levels are easily and rapidly determined by most hospital laboratories and, depending on the method used, are accurate and specific.
- ✓ In general, there is only rough correlation between blood levels and clinical presentation; however, an ethanol level below 300 mg/dL in a comatose patient should initiate a search for alternative causes.
- ✓ If ethanol levels are not readily available, the ethanol concentration maybe estimated by calculating the osmolar gap (see chapter 1).
- **Suggested laboratory studies:** include glucose, electrolytes, BUN, creatinine, liver transaminases, PT, magnesium, arterial blood gases or oximetry, and chest x-ray (if pulmonary aspiration is suspected). Consider CT scan of the head if the patient has focal neurological deficits or altered mental status inconsistent with the degree of blood alcohol elevation.

- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ **Acute intoxication.** Treatment is mainly supportive: (i) protect the airway to prevent aspiration and intubate and assist ventilation if needed (chapter 1); (ii) give glucose and thiamine (chapter 3), treat coma (chapter 1) and seizures (chapter 1) if they occur; (iii) treat hypoglycemia with iv glucose 0.5 to 1 g/kg. Glucagon is not effective for alcohol induced hypoglycemia; and (iv) correct hypothermia with gradual rewarming (chapter 1). Most patients will recover within 4–6 h. Observe children until their blood alcohol level is below 50 mg/dL and there is no evidence of hypoglycemia.
  - ✓ **Alcoholic ketoacidosis:** treat with volume replacement, thiamine (chapter 3), and supplemental glucose (chapter 3). Most patients recover rapidly. Long-term drinkers are sometimes treated with IV fluids containing magnesium, folate, thiamine, and multivitamins. Wernicke's encephalopathy is characterized by abnormal mental status, ataxia, and nystagmus, and requires daily treatment with thiamine, 100 mg, until normal diet is resumed.
  - ✓ For metabolic acidosis, give 0.5–1 mEq/kg IV bolus of sodium bicarbonate; repeat as needed to correct serum pH to at least 7.2.
  - ✓ **Alcohol withdrawal:** treat with benzodiazepines (e.g., diazepam, 2–10 mg iv initially, repeated as needed; see chapter 3).

- **Specific drugs and antidotes:** there is no available specific ethanol antagonist, despite anecdotal reports of arousal after administration of naloxone.
- **Decontamination**
- ✓ **Prehospital:** do not induce vomiting or administer activated charcoal.
- ✓ **Hospital:** because ethanol is rapidly absorbed, gastric lavage is usually not indicated unless other drug ingestion is suspected. Consider lavage only if the alcohol ingestion was massive and recent (within 30–45 min).
- ✓ Activated charcoal does not effectively adsorb ethanol but may begiven if other toxins were ingested.
- **Enhanced elimination:** metabolism of ethanol normally occurs at a fixed rate of approximately 20–30 mg/dL/h. Elimination rates are faster in chronic alcoholics and at serum levels above 300 mg/dL. Hemodialysis efficiently removes ethanol, but enhanced removal is rarely needed because supportive care is usually sufficient. Hemoperfusion and forced diuresis are not effective.

## NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The nonsteroidal anti-inflammatory drugs (NSAIDs) are a chemically diverse group of agents that share similar pharmacologic properties and are widely used for control of pain and inflammation. Overdose by most of the agents in this group usually produces only mild gastrointestinal upset.

- **Mechanism of toxicity:** NSAIDs produce their pharmacologic and most toxicologic effects by inhibiting the enzyme cyclooxygenase. This results in decreased production of prostaglandins and decreased pain and inflammation. CNS, hemodynamic, pulmonary, and hepatic dysfunction also occur with some agents, but the relationship to prostaglandin production remains uncertain. Prostaglandins are also involved in maintaining the integrity of the gastric mucosa and regulating renal blood flow. Thus, acute or chronic intoxication may affect these organs.
- **Pharmacokinetics:** NSAIDs are generally well-absorbed, and Vd values are relatively small (e.g., 0.15 L/kg for ibuprofen). Most agents' are highly protein bound, and most are eliminated through hepatic metabolism and renal excretion with variable half-lives (e.g., 1.5–2.5 hs for ibuprofen and 13–15h for naproxen).

- **Toxic dose:** human data are insufficient to establish a reliable correlation between amount ingested, plasma concentrations, and clinical toxic effects. Generally, significant symptoms occur after ingestion of more than 5–10 times the usual therapeutic dose.
- **Clinical presentation:** in general, patients with NSAID overdose are asymptomatic or have mild gastrointestinal upset (nausea, vomiting, abdominal pain, and sometimes hematemesis). Occasionally, patients exhibit drowsiness, lethargy, ataxia, nystagmus, tinnitus, and disorientation. With the more toxic agents and with massive **ibuprofen** overdose, seizures, coma, renal failure, and cardiorespiratory arrest may occur. Hepatic dysfunction, hypoprothrombinemia, and metabolic acidosis are also commonly reported.
- **Diagnosis:** is usually based primarily on history of ingestion of NSAIDs, because symptoms are mild and non-specific and quantitative levels are not usually available.
  - **Specific levels:** are not usually readily available and do not contribute to clinical management.
  - **Other useful laboratory studies:** include CBC, electrolytes, glucose, BUN, creatinine, liver transaminases, PT, and urinalysis.
- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary (see chapter 1).
  - ✓ Administer supplemental oxygen.
  - ✓ Treat seizures (chapter 1), coma (chapter 1), and hypotension (chapter 1) if they occur.
  - ✓ Antacids may be used for mild gastrointestinal upset. Replace fluid losses with IV crystalloid solutions.
  - **Specific drugs and antidotes:** there is no antidote. Vitamin K (see chapter 3) may be used for patients with elevated PT caused by hypoprothrombinemia.
  - **Decontamination**
  - ✓ **Prehospital:** consider activated charcoal if available and the patient is alert.
  - ✓ **Hospital:** consider activated charcoal. Gastric emptying is not necessary for most ingestion, if activated charcoal can be given promptly. Consider gastric lavage for massive overdoses.
  - **Enhanced elimination:** NSAIDs are highly protein bound and extensively metabolized. Thus, hemodialysis, peritoneal dialysis, and forced diuresis are not likely to be effective.

**Charcoal hemoperfusion** may be effective for **phenylbutazone** overdose, although there are limited clinical data to support its use.

- There are no data on the use of repeat-dose activated charcoal therapy.

## OPIATES AND OPIOIDS

Include naturally occurring opiates (e.g., morphine, heroin, codeine, and hydrocodone) as well as new totally synthetic opiate analogues (e.g., fentanyl, meperidine/pethidine, and methadone (Table 2.6). A wide variety of prescription medications contain opioids, often in combination with aspirin or acetaminophen. **Dextromethorphan** (see chapter 2) is an opioid derivative with potent antitussive but no analgesic or addictive properties. **Tramadol** is a newer analgesic that is unrelated chemically to the opiates but acts on mu (μ) opioid receptors.

- **Mechanism of toxicity:** in general, opioids share the ability to stimulate a number of specific opiate receptors in the CNS, causing sedation and respiratory depression. Death results from respiratory failure, usually as a result of apnea or pulmonary aspiration of gastric contents. In addition, acute noncardiogenic pulmonary edema may occur by unknown mechanisms.
- **Pharmacokinetics:** usually, peak effects occur within 2–3 h, but absorption may be slowed by their pharmacologic effects on gastrointestinal motility. The timing of peak effects is related to the mode of ingestion. When used iv, peak effects are in 10-20 min. Oral dosing gives peak effects in 1-2 h. Nasal absorption leads to peak effects in 15-30 min. Most drugs have large Vd (3–5 L/kg). The rate of elimination is highly variable, from 1–2 h for fentanyl derivatives versus 15–30 h for methadone.
- **Toxic dose:** the toxic dose varies widely depending on the specific compound, the route and rate of administration, and tolerance to the effects of the drug as a result of chronic use. Some newer fentanyl derivatives have potency up to 2000 times that of morphine.
- **Clinical presentation**
  - **With mild or moderate overdose:** lethargy is common. The pupils are usually small, often "pinpoint" size. Blood pressure and pulse rate are decreased, bowel sounds are diminished, and the muscles are usually flaccid.
  - **With higher doses:** coma is accompanied by respiratory depression, and apnea often results in sudden death. Noncardiogenic pulmonary edema may occur, often after resuscitation and administration of the opiate antagonist naloxone.

- **Seizures:** are not common after opioid overdose but occur occasionally with certain compounds (e.g., dextromethorphan, meperidine, propoxyphene, and tramadol). Seizures may occur in patients with renal impairment who receive repeated doses of meperidine, owing to accumulation of the metabolite normeperidine.
- **Cardiotoxicity:** similar to that seen with tricyclic antidepressants and quinidine can occur in patients with severe **propoxyphene** intoxication.
- Some newer synthetic opioids have mixed agonist and antagonist effects withunpredictable results in overdose.
- Opioid **withdrawal syndrome** can cause anxiety, piloerection (goosebumps), abdominal cramps and diarrhea, and insomnia.

- **Diagnosis:** is simple when typical manifestations of opiate intoxication are present (pinpoint pupils and respiratory and CNS depression), and the patient quickly awakens after administration of naloxone. Signs of iv drug abuse (e.g., needle track marks) may be present.
  - **Specific levels:** are not usually performed because of poor correlation with clinical effects. Qualitative screening of the urine is an effective way to confirm recent use. Fentanyl derivatives, tramadol, and some other synthetic opioids may not be detected by routine toxicologic screens.
  - **Other useful laboratory studies:** include electrolytes, glucose, arterial blood gases or oximetry, chest x-ray, and stat serum acetaminophen or salicylate levels (if the ingested overdose was of a combination product).

**Table 2.6: Common opiates and opoids[a]**

| Drug | Type of activity | Usual adult dose* (mg) | Elimination half life (h) | Duration of analgesia (h) |
|---|---|---|---|---|
| Codein | Agonist | 60 | 2-4 | 4-6 |
| Fentanyl | Agonist | 0.2 | 1-5 | 0.5-2 |
| Meperidine | Agonist | 100 | 2-5 | 2-4 |
| Methadone | Agonist | 10 | 20-30 | 4-8** |
| Morphine | Agonist | 10 | 2-4 | 3-6 |
| Pentazocin | Mixed | 50 | 2-3 | 2-3 |

*Usual dose: Dose equivalent to 10 mg of morphine.
**Sedation and coma may last 2–3 days

- **Treatment**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary (see Chapter 1).
  - ✓ Administer supplemental oxygen.
  - ✓ Treat coma (chapter 1), seizures (chapter 1), hypotension (chapter 1), and noncardiogenic pulmonary edema (chapter 1) if they occur.
  - **Specific drugs and antidotes**
  - ✓ **Naloxone** (chapter 3) is a specific opioid antagonist with no agonist properties of its own; large doses may be given safely. Administer naloxone, 0.4–2 mg iv. As little as 0.2–0.4 mg is usually effective for heroin overdose. Repeat doses every 2–3 min, if there is no response, up to a total dose of 10–20 mg if an opioid overdose is strongly suspected. ***Caution:*** the duration of effect of naloxone (1–2 h) is shorter than that of many opioids. Therefore, do not release the patient who has awakened after naloxone treatment until at least 3–4 h have passed since the last dose of naloxone. In general, if naloxone was required to reverse opioid-induced coma, it is safer to admit the patientfor at least 6–12 h of observation.
  - ✓ **Sodium bicarbonate** (chapter 3) may be effective for QRS interval prolongation or hypotension associated with propoxyphene poisoning.
  - **Decontamination** (see chapter 1)
  - ✓ **Prehospital:** general supportive care
  - ✓ **Hospital:** administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly.
  - **Enhanced elimination:** because of the very large Vd of opioids and the availability of an effective antidotal treatment, there is no role for enhanced elimination procedures.

## PHENOTHIAZINES AND OTHER ANTIPSYCHOTIC DRUGS

Phenothiazines, butyrophenones, and other related drugs (Table 2.7) are widely used to treat psychosis and agitated depression. In addition, some of these drugs (e.g., prochlorperazine, promethazine, and droperidol) are used as antiemetic agents. Suicidal overdoses are common, but because of the high toxic-therapeutic ratio, acute overdose seldom results in death. A large number of newer agents have been developed. However, overdose experience with these agents is limited.

- **Mechanism of toxicity:** a variety of pharmacologic effects are responsible for toxicity involving primarily the cardiovascular and central nervous systems.
  - **Cardiovascular:** anticholinergic effects produce tachycardia. Alpha-adrenergic blockade causes orthostatic hypotension. With very large overdoses ofsome agents, quinidine-like membrane-depressant effects on the heart may occur.
  - **Central nervous system:** centrally mediated sedation and anticholinergic effects contribute to CNS depression. Alpha-adrenergic blockade causes small pupils, despite anticholinergic effects on other systems. Extrapyramidal dystonic reactions are relatively common with therapeutic doses and are probably caused by central dopamine receptor blockade. The seizure threshold may be lowered by unknown mechanisms. Temperature regulation is also disturbed, resulting in poikilothermia
- **Pharmacokinetics:** these drugs have large Vd (10–30L/kg), and most have long elimination half-lives (e.g., chlorpromazine = 18–30 h). Elimination is largely by hepatic metabolism. Typical daily doses are given in Table 2.7.
- **Toxic dose:** extrapyramidal reactions, anticholinergic side effects, and orthostatic hypotension are often seen with therapeutic doses. Tolerance to the sedating effects of the antipsychotics is well-described, and patients on chronic therapy may tolerate much larger doses than other persons.. The toxic dose after acute ingestion is highly variable. Serious CNS depressionand hypotension may occur after ingestion of 200–1000 mg of chlorpromazinein children or 3–5 g in adults.

**Table II–7: Common Phenothiazines and other antipsychotic drugs**

| Drug | Usual adult daily dose (mg) | Toxicity |
|---|---|---|
| Chlorpromazine | 200–2000 | E, A, H |
| Haloperidol | 1–100 | E |
| Promethazine* | 25-200 | A, E |

E = Extrapyramidal reactions; A = Anticholinergic effects; H = Hypotension.
*Used primarily as an antiemetic

- **Clinical presentation:** major toxicity is manifested in the cardiovascular and CNS. Also, anticholinergic intoxication (see chapter 1) may occur as a result of ingestion of benztropine (Cogentin) or other co-administered drugs.

- **Mild intoxication:** causes sedation, small pupils, and orthostatic hypotension. Anticholinergic manifestations include dry mouth, absence of sweating, tachycardia, and urinary retention. Paradoxically, clozapine causes hypersalivation through an unknown mechanism.
- **Severe intoxication:** may cause coma, seizures, and respiratory arrest. The ECG usually shows QT interval prolongation and occasionally QRS prolongation (particularly with thioridazine). Hypothermia or hyperthermia may occur. Clozapine can cause a prolonged confusional state and rarely cardiac toxicity. Risperidone can cause QT interval prolongation, but delirium is less severe.
- **Extrapyramidal** dystonic side effects of therapeutic doses include torticollis, jaw muscle spasm, oculogyric crisis, rigidity, bradykinesia, and pill-rolling tremor.
- Patients on chronic antipsychotic medication may develop the **neuroleptic malignant syndrome** characterized by rigidity, hyperthermia, sweating, lactic acidosis, and rhabdomyolysis.
- Clozapine use has been associated with agranulocytosis.

- **Diagnosis:** is based on history of ingestion and findings of sedation, small pupil, hypotension, and QT interval prolongation. Dystonias in children should always suggest the possibility of antipsychotic exposure, often as a result of intentional administration by parents. Phenothiazines are occasionally visible on plain abdominal x-rays.
  - **Specific levels:** quantitative blood levels are not routinely available and do not help in diagnosis or treatment. Qualitative screening may easily detect phenothiazines in urine or gastric juice, but butyrophenones such as haloperidol are usually not included in toxicologic screens.
  - **Other useful laboratory studies:** include electrolytes, glucose, BUN, creatinine, CPK, arterial blood gases or oximetry, abdominal x-ray (to look for radiopaque pills), and chest x-ray.
- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary.
  - ✓ Administer supplemental oxygen.
  - ✓ Treat coma, seizures, hypotension, and hyperthermia if they occur.

- ✓ Monitor vital signs and ECG for at least 6 h, and admit the patient for at least 24 h if there are signs of significant intoxication. Children with antipsychotic intoxication should be evaluated for possible intentional abuse.
- ➢ **Specific drugs and antidotes:** there is no specific antidote.
- ✓ **Dystonic reactions:** give **diphenhydramine**, 0.5–1 mg/kg im or iv (see chapter 3) or benztropine (see chapter 3).
- ✓ **QRS interval prolongation:** treat quinidine-like cardiotoxic effects with **bicarbonate**, 1–2 mEq/kg iv (see chapter 3).
- ➢ **Decontamination**
- ✓ **Prehospital:** general supportive measures
- ✓ **Hospital:** consider activated charcoal if the patient has no altered mental staus and if s/he could protect the airway and come with in 1 h. Gastric emptying is not necessary if activated charcoal can be given promptly.
- ➢ **Enhanced elimination:** owing to extensive tissue distribution, these drugs are not effectively removed by dialysis or hemoperfusion. Repeat-dose activated charcoal has not been evaluated.

## PHENYTOIN

Phenytoin is used orally for the prevention of generalized (grand mal) and psychomotor seizures. Intravenous phenytoin is used to treat status epilepticus and occasionally as an antiarrhythmic agent. Oral formulations include suspensions, capsules, and tablet preparations. The brand Dilantin Kapseals exhibits delayed absorption characteristics not usually shared by generic products.

- **Mechanism of toxicity:** toxicity may be caused by the phenytoin itself or by the propylene glycol diluent used in parenteral preparations.
  - ➢ **Phenytoin:** alters neuronal ion fluxes, increasing refractory periods and decreasing repetitive neuronal firing. It is also known to increase brain concentrations of GABA. Toxic levels usually cause CNS depression.
  - ➢ The **propylene glycol** diluent in parenteral preparations may cause myocardial depression and cardiac arrest when infused rapidly (> 40–50 mg/min [0.5–1 mg/kg/min]). The mechanism is not known.

- **Pharmacokinetics:** absorption may be slow and unpredictable. The time to peak plasma levels varies with the dosage. The Vd is about 0.5–0.8 L/kg. Protein binding is about 90% at therapeutic levels. Hepatic elimination is saturable (zero-order kinetics) at levels near the therapeutic range, so the apparent "half-life" increases as levels rise (26 h at 10mg/L, 40 h at 20 mg/L, and 60 h at 40 mg/L).
- **Toxic dose:** the minimum acute toxic oral overdose is approximately 20 mg/kg. Because phenytoin exhibits dose-dependent elimination kinetics, accidental intoxication can easily occur in patients on chronic therapy owing to drug interactions or slight dosage adjustments.
- **Clinical presentation:** toxicity caused by phenytoin may be associated with acute oral overdose or chronic accidental overmedication. In acute oral overdose, absorption and peak effects may be delayed.
  - **Mild to moderate intoxication:** commonly causes nystagmus, ataxia, and dysarthria. Nausea, vomiting, diplopia, hyperglycemia, agitation, and irritability have also been reported.
  - **Severe intoxication:** can cause stupor, coma, and respiratory arrest. Although seizures have been reported, literature reports are unconvincing; seizures in a phenytoin-intoxicated patient should prompt a search for other causes (e.g., anoxia, hyperthermia, or an overdose of another drug).
  - **Rapid intravenous injection** usually at rates exceeding 50 mg/min, can cause profound hypotension, bradycardia, or cardiac arrest. Cardiac toxicity does not occur with oral overdose.
- **Diagnosis:** is based on history of ingestion or is suspected in any epileptic patient with altered mental status or ataxia.
  - **Specific levels:** serum phenytoin concentrations are generally available in all hospital clinical laboratories. Obtain repeated blood samples because slow absorption may result in delayed peak levels. The therapeutic concentrationrange is 10–20 mg/L. Above 20 mg/L, nystagmus is common. Above 30 mg/L, ataxia, slurred speech, and tremor are common. With levels higher than 40 mg/L, lethargy, confusion, and stupor ensue. Survival has been reported in three patients with levels above 100 mg/L. Because phenytoin is protein bound, patients with renal failure or hypoalbuminemia may

experience toxicity at lower serum levels. Free (unbound) serum phenytoin levels are not routinely available.

- **Other useful laboratory studies:** include electrolytes, glucose, BUN, creatinine, serum albumin, and ECG monitoring (during iv infusion).

- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary (see chapter 1).
  - ✓ Administer supplemental oxygen.
  - ✓ Treat stupor and coma (chapter 1) if they occur. Protect the patient from self injury caused by ataxia.
  - ✓ If seizures occur, consider an alternative diagnosis and treat with other usual anticonvulsants (chapter 1).
  - ✓ If hypotension occurs with iv phenytoin administration, immediately stop the infusion and administer iv fluids and pressors (chapter 1) if necessary.
  - **Specific drugs and antidotes:** there is no specific antidote.
  - **Decontamination** (see chapter 1)
  - ✓ **Prehospital:** administer activated charcoal if available. Ipecac-induced vomiting may be useful for initial treatment at the scene (e.g., children at home) if it can be given within a few minutes of exposure.
  - ✓ **Hospital:** administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly.
  - **Enhanced elimination:** repeat-dose activated charcoal (see chapter 1) may enhance phenytoin elimination. There is no role for diuresis, dialysis, or hemoperfusion.

## TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants are commonly taken in overdose by suicidal patients' and represent a major cause of poisoning hospitalizations and deaths. Currently available tricyclic antidepressants are described in Table 2.8.

**TABLE 2.8: TRICYCLIC ANTIDEPRESSANTS**

| S. No. | Drug | Usual adult dose (mg) | Usual half-life (h) | Toxicity* |
|---|---|---|---|---|
| 1. | Amitriptyline | 75–200 | 9-25 | A, C, S |
| 2. | Clomipramine | 100–250 | 20–40 | A, C, S |
| 3. | Imipramine | 75–200 | 11–25 | A, C, S |

*A = anticholinergic; C = cardiovascular; S = seizures.

- **Mechanism of toxicity:** tricyclic antidepressant toxicity affects primarily the cardiovascular and central nervous systems.
  - **Cardiovascular effects:** several mechanisms contribute to cardiovascular toxicity.
  - ✓ Anticholinergic effects and inhibition of neuronal reuptake of catecholamines result in tachycardia and mild hypertension.
  - ✓ Peripheral alpha-adrenergic blockade induces vasodilation.
  - ✓ Membrane-depressant (quinidine-like) effects cause myocardial depression and cardiac conduction disturbances by inhibition of the fast sodium channel that initiates the cardiac cell action potential. Metabolic or respiratory acidosis may contribute to cardiotoxicity by further inhibiting the fast sodium channel.
  - **Central nervous system effects:** these result in part from anticholinergic toxicity (e.g., sedation and coma), but seizures are probably a result of inhibition of reuptake of norepinephrine or serotonin in the brain or other central effects.
- **Pharmacokinetics:** anticholinergic effects of the drugs may retard gastric emptying, resulting in slow or erratic absorption. Most of these drugs are extensively bound to body tissues and plasma proteins, resulting in very large Vd and long elimination half-lives. Tricyclic antidepressants are primarily metabolized by the liver, with only a small fraction excreted unchanged in the urine. Active metabolites may contribute to toxicity; several drugs are metabolized to other well-known tricyclic antidepressants (e.g., amitriptyline to nortriptyline and imipramine to desipramine).
- **Toxic dose:** most of the tricyclic antidepressants have narrow therapeutic index so that doses of less than 10 times the therapeutic daily dose may produce severe intoxication. In general, ingestion of 10–20 mg/kg is potentially life threatening.

- **Clinical presentation:** triyclic antidepressant poisoning may produce any of three major toxic syndromes: anticholinergic effects, cardiovascular effects, and seizures. Depending on the dose and the drug, patients may experience some or all of these toxic effects. Symptoms usually begin within 30–40 min of ingestion but may be delayed owing to erratic gut absorption. Patients who are initially awake may abruptly lose consciousness or develop seizures without warning.
  - **Anticholinergic** effects: include sedation, delirium, coma, dilated pupil, dry skin and mucous membranes, diminished sweating, tachycardia, diminished or absent bowel sounds, and urinary retention. Myoclonic or myokymic jerking is common with anticholinergic intoxication and may be mistaken for seizure activity.
  - **Cardiovascular** toxicity manifests as abnormal cardiac conduction, arrhythmias, and hypotension.
    - ✓ Typical electrocardiographic findings include sinus tachycardia with prolongation of the PR, QRS, and QT intervals. Various degrees of AV block may be seen. Prolongation of the QRS complex to 0.12s or longer is a fairly reliable predictor of serious cardiovascular and neurologictoxicity (except in the case of amoxapine, which causes seizures andcoma with no change in the QRS interval).
    - ✓ Sinus tachycardia accompanied by QRS interval prolongation may resemble ventricular tachycardia. True ventricular tachycardia and fibrillation may also occur. Atypical or polymorphous ventricular tachycardia (torsades de pointes) associated with QT interval prolongation may occur with therapeutic dosing, but is actually uncommon in overdose. Development of bradyarrhythmias usually indicates a severely poisoned heart and carries a poor prognosis.
    - ✓ Hypotension caused by venodilation is common and usually mild. In severe cases, hypotension results from myocardial depression and may be refractory to treatment; some patients die with progressive intractable cardiogenic shock. Pulmonary edema is also common in severe poisonings.
  - **Seizures** are common with tricyclic antidepressant toxicity and may be recurrentor persistent. The muscular hyperactivity from seizures and myoclonicjerking, combined with diminished sweating, can lead to severe hyperthermia (see chapter 1), resulting in rhabdomyolysis, brain damage, multisystem failure, and death.

- **Death** from tricyclic antidepressant overdose usually occurs within a few hours of admission and may result from ventricular fibrillation, intractable cardiogenic shock, or status epilepticus with hyperthermia. Sudden death several days after apparent recovery has occasionally been reported, but in all such cases there was evidence of continuing cardiac toxicity within 24 h of death.

- **Diagnosis:** tricyclic antidepressant poisoning should be suspected in any patient with lethargy, coma, or seizures accompanied by QRS interval prolongation. QRS interval prolongation greater than 0.12 s in the limb leads suggests severe poisoning.
  - **Specific levels**
  - ✓ Plasma levels of some of the tricyclic antidepressants can be measured by clinical laboratories. Therapeutic concentrations are usually less than 0.3μg/mL (300 ng/mL). Total concentrations of parent drug plus metabolite of 1 μg/mL (1000 ng/mL) or greater are usually associated with serious poisoning. Generally, plasma levels are not used in emergency management because the QRS interval and clinical manifestations of overdose are reliable and more readily available indicators of toxicity.
  - ✓ Most tricyclics are detectable on comprehensive urine toxicology screening. Some rapid immunologic techniques are available and have sufficiently broad cross-reactivity to detect several tricyclics. However, use ofthese assays for rapid screening in the hospital laboratory is not recommended because they may miss some important drugs and give positive results for others present in therapeutic concentrations.
  - **Other useful laboratory studies:** include electrolytes, glucose, BUN, creatinine, CPK, urinalysis for myoglobin, arterial blood gases or oximetry, 12-lead ECG and continuous ECG monitoring, and chest x-ray.

- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary (see chapter 1).
  - ✓ ***Caution:*** respiratory arrest can occur abruptly and without warning.
  - ✓ Treat coma (chapter 1), seizures (chapter 1), hyperthermia (chapter 1), hypotension (chapter 1), and arrhythmias (chapter 1) if they occur. ***Note:*** Do not use procainamide or other Type Ia or Ic antiarrhythmic agents for ventricular tachycardia, because these drugs may aggravate cardiotoxicity.

- ✓ Consider cardiac pacing for bradyarrhythmias and high-degree AV block, and overdrive pacing for Torsades de pointes.
- ✓ Mechanical support of the circulation (e.g., cardiopulmonary bypass) maybe useful (based on anecdotal reports) to stabilize patients with refractory shock, allowing time for the body to eliminate some of the drug.
- ✓ If seizures are not immediately controlled with usual anticonvulsants, paralyze the patient with a neuromuscular blocker such as pancuronium to prevent hyperthermia, which may induce further seizures, and lactic acidosis, which aggravates cardiotoxicity. ***Note:*** paralysis abolishes the muscular manifestations of seizures, but has no effect on brain seizure activity. After paralysis, ECG monitoring is necessary to determine the efficacyof anticonvulsant therapy.
- ✓ Continuously monitor the temperature, other vital signs, and ECG in asymptomatic patients for a minimum of 6 h, and admit patients to an intensive care setting for at least 24 h if there are any signs of toxicity.

- ➢ **Specific drugs and antidotes**

- ✓ In patients with QRS interval prolongation or hypotension, administer **sodium bicarbonate**, 1–2 mEq/kg iv, and repeat as needed to maintain the arterial pH between 7.45 and 7.55. Sodium bicarbonate may reverse membrane-depressant effects by increasing extracellular sodium concentrations and by a direct effect of pH on the fast sodium channel.
- ✓ Hyperventilation, by inducing a respiratory alkalosis (or reversing respiratory acidosis), may also be of benefit but works only transiently and may provoke seizures.
- ✓ **NB:** Although **physostigmine** has been widely advocated in the past, it should ***not*** be routinely administered to patients with tricyclic antidepressant poisoning. It may aggravate conduction disturbances, causing asystole, further impair myocardial contractility, worsening hypotension, and contribute to seizures.

- ➢ **Decontamination** (see chapter 1)

- ✓ **Prehospital:** administer activated charcoal if available. Do ***not*** induce vomiting because of the risk of abrupt onset of seizures.

- ✓ **Hospital:** administer activated charcoal. Perform gastric lavage for large ingestions (e.g., > 20–30 mg/kg). Gastric emptying is probably not necessaryfor smaller ingestions if activated charcoal can be given promptly.

- ➢ **Enhanced elimination:** owing to extensive tissue and protein binding with a resulting large Vd, dialysis and hemoperfusion are not effective. Although repeat-dose charcoal has been reported to accelerate tricyclic antidepressant elimination, the data are not convincing.

## HERBAL MEDICINES

Although most plant exposures are unintentional, many adults ingest herbal products for self-treatment of illness and for health maintenance. What constitutes an herbal product is generally ill-defined and, though the term implies a leafy plant, herbal products may contain non-herb plant materials, animal products, and/or mineral products.While many herbal products are innocuous or possess minimal toxicity, some contain toxic ingredients that may not be identified on the label. These unidentified ingredients may be unintentionally included in the product (e.g., misidentification of a toxic plant as a desired nontoxic plant or contamination with pesticide residues or heavy metals) or adulterants introduced for increased effect (e.g., addition of a pharmaceutical agent to an herbal preparation). Besides toxicity from natural products contained in some medicinal plants, "herbal" or "traditional" preparations may sometimes actually contain allopathic drugs such as phenylbutazone, corticosteroids, salicylates, ephedrine, or toxic metal salts such as mercury lead or arsenic.

- **Mechanism of toxicity:** herbal products are categorized in Groups as 1, 2a, 2b, and 3.
  - ➢ **Group 1** plants: contain systemically active poisons that may cause serious intoxication.
  - ➢ **Group 2a** plants: contain insoluble calcium oxalate crystals that cause burning pain and swelling of mucous membranes.
  - ➢ **Group 2b** plants: contain soluble oxalate salts (sodium or potassium) that can produce acute hypocalcemia, renal injury, and other organ damage secondary to precipitation of calcium oxalate crystals in various organs. Mucous membrane irritation and gastroenteritis may also occur.
  - ➢ **Group 3** plants: contain various chemical agents that generally produce only mild to moderate gastrointestinal irritation after ingestion or dermatitis after skin contact.

- **Toxic dose**
  - Plants: the amount of toxin ingested is usually unknown. Concentrations of the toxic agent may vary depending on the plant part, the season, and soil conditions. In general, childhood ingestion of a single leaf or a few petals from even Group 1 plants results in little or no toxicity because of the small amountof toxin absorbed.
  - Herbs; herbal teas and medications may contain variable amounts of active or poisonous substances. Homeopathic medicines are usually extremely diluted, and toxicity is rare. On the other hand, naturopathic medicines may be highly concentrated. In addition, commercial packaged products ("patent" medicines or nutritional supplements) may contain multiple different herbal and mineral products in various concentrations. Nutritional supplements may contain toxic plants or herbal medicines. Contamination or adulteration with unlabelled substances may also be present.
- **Clinical presentation**
  - **Group 1:** the presentation depends upon the active toxic agent. In most cases, vomiting, abdominal pain, and diarrhea occur within 60–90 min of a significant ingestion. With some toxins (e.g., ricin), severe gastroenteritis may result in massive fluid and electrolyte loss.
  - **Group 2a:** insoluble calcium oxalate crystals cause immediate burning, prickly pain upon contact with mucous membranes. Swelling of the lips, tongue, and pharynx may occur, and in rare cases glottic edema may result in airway obstruction. Symptoms usually resolve within a few hours.
  - **Group 2b:** soluble oxalates may be absorbed into the circulation, where they precipitate with calcium, resulting in acute hypocalcemia and multiple-organ injury, including renal tubular necrosis.
  - **Group 3:** skin or mucous membrane irritation may occur, although it is less severe than with Group 2 plants. Vomiting and diarrhea are common but are usually mild and self-limited. Fluid and electrolyte imbalances caused by severe gastroenteritis are rare.
- **Diagnosis:** is usually based on history of exposure and is suspected when plant material is seen in vomitus. Identification of the plant is essential for proper treatment. Because common names sometimes refer to more than one plant, it is preferable to confirm the botanical name.

- **Specific levels:** serum toxin levels are not available for most plant toxins. In selected cases, laboratory analyses for therapeutic drugs may be used (e.g., digoxin assay for oleander glycosides).
- **Other useful laboratory studies:** include, for patients with gastroenteritis, CBC, electrolytes, glucose, BUN, creatinine, and urinalysis. If hepatotoxicity is suspected, also obtain liver transaminases and PT.

- **Treatment:** most ingestions cause no symptoms or only mild gastroenteritis, and patients recover quickly with supportive care.
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary.
  - ✓ Administer supplemental oxygen.
  - ✓ Treat coma, seizures, arrhythmias, and hypotensionif they occur.
  - ✓ Replace fluid losses caused by gastroenteritis with intravenous crystalloidsolutions.
  - **Specific drugs and antidote:** there are few effective antidotes.
  - **Decontamination**
  - ✓ **Group 1 and Group 2b plants**
  - ❖ **Prehospital:** administer activated charcoal if available. Ipecac-induced vomiting may be useful for initial treatment at the scene (e.g., children at home) if it can be given within a few minutes of exposure.
  - ❖ **Hospital:** administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly.
  - ✓ **Group 2a and Group 3 plants**
  - ❖ Wash the affected areas with plain water and give water or milk to drink.
  - ❖ Do ***not*** induce vomiting, because of potential aggravation of irritant effects.
  - ❖ Gastric lavage and activated charcoal are not necessary.
  - **Enhanced elimination:** these procedures are not generally effective.

## CAUSTICS AND CORROSIVES

Corrosives include acidic, alkaline, or rarely, have neutral pH (e.g., silver nitrate, concentrated hydrogen peroxide). The burning sensation inhibit from consuming much of the product. Because liquids do not stick, they are taken better than solid and can damage the whole esophagus. Liquids also may be aspirated into the airways, leading to air way obstruction.

- **Mechanism of toxicity:** alkali burns more common and worse than acid. Acid causes a coagulation-type necrosis. In contrast, alkalis' cause a liquefactive necrosis that continues penetration into deeper tissues, resulting in extensive damage than acidic burns. Button batteries lead to espophageal perforation via leakage of the corrosive metal salts by direct impaction of the disk-shaped foreign body, and possibly by local discharge of electrical current at the site of impaction.
- **Toxic dose**: there is no specific toxic dose or level.
- **Clinical presentation**
  - **After ingestion** of corrosive, hyper salivation, lethargy, polydipsia, vomiting, abdominal pain, dysphagia, pharyngeal edema, oral pain, drooling, and oral, esophageal, and/or gastric ulceration could occur.
  - **Inhalation of** corrosive gases may cause upper respiratory tract injury, with stridor, hoarseness, wheezing, and noncardiogenic pulmonary edema.
  - **Eye or skin exposure** to corrosive causes instant pain and redness, followed by blistering. Conjunctivitis and lacrimation are common. Serious full-thickness burns and blindness can occur.
- **Diagnosis:** is based on history of exposure to a corrosive agent and characteristic findings of skin, eye, or mucosal irritation and the presence of injury to the gastrointestinal tract.
  - **Endoscopy:** esophageal or gastric injury is unlikely after ingestion if the patient is completely asymptomatic, but small number of patients will have injury in the absence of oral burns or obvious dysphagia. Endoscopy for all patients regardless of symptoms may be necessary.
  - **X-rays:** of the chest and abdomen will show impacted button batteries, pneumomediastinum from esophageal perforation or free abdominal air from gastric perforation.
  - **Specific levels:** depend on the specific chemical.
  - **Other investigations studies:** CBC, electrolytes, glucose, arterial blood gases, chest x-ray, and upright abdominal x-ray.
- **Treatment**
  - **Emergency and supportive measures**

- ✓ Inhalation**: give** oxygen, and follow closely for signs of airway obstruction or for non-cardiogenic pulmonary edema.
- ✓ Chemical ingestion**: Prehospital;** immediately give water or milk to drink. Do ***not*** induce vomiting or pH-neutralizing agents (e.g., dilute vinegar or bicarbonate)**, or g**astric lavage. Give activated charcoal if the ingested agent can cause significant systemic toxicity. If there is espoageal perforation, avoid giving water as it may also enter to the medistnum. If esophageal or gastric perforation is suspected refer immediately. For most agents, there is no specific antidote.
- ✓ Chemical eye and skin burn**:** remove all clothing and wash skin and irrigate eyes with copious water or saline.
- ✓ **Button batteries:** lodged immediately endoscopy guided removal should be done immediately.

## DETERGENTS

Detergents are synthetic surface active agent containing chemical products used at home. Most products contain bleaching (chlorine-releasing), bacteriostatic (having a low concentration of quaternary ammonium compound), or enzymatic agents.

- **Mechanism of toxicity**: detergents may precipitate and denature proteins, are irritating to tissues, and possess keratolytic and corrosive actions. Detergents may cause skin irritation and have sensitizing properties.
- **Toxic dose**: - No minimum or lethal toxic doses have been established. Mortality and serious morbidity are rare.
- **Clinical presentation**: nausea, vomiting, and diarrhea, may cause hematemesis as a result secondary dehydration and electrolyte imbalance may develop. Mild ocular irritation is possible. Large ingestions may produce intractable vomiting, diarrhea, and hematesis. Dermal contact generally causes a mild erythema or rash.
- **Diagnosis**: based on history of exposure.
  - ➢ Specific levels: there are no specific blood or urine levels.
  - ➢ Other useful laboratory studies include electrolytes, glucose, calcium andphosphate (after ingestion of phosphate-containing products), and methemoglobin (Cationic detergents).
- **Treatment**

- In patients with protracted vomiting or diarrhea, administer IV fluids to correct dehydration and electrolyte imbalance. If corrosive injury, use the management guideline for corrosive ingestion. If hypocalcemia occurs after ingestion of a phosphate-containing product, give iv calcium.
- **Decontamination:** dilute orally with small amounts of water or milk. Do not induce vomiting because of the risk for corrosive injury. Consider gastric lavage only for massive ingestions, activated charcoal is not effective. In severe cases anti-emetics may be required (e.g., metoclopramide, 0.2–0.4 mg/kg, PO, SC, or IM, qid based).
- Eyes and skin exposure: irrigate with copious amounts of tepid water or saline. Consult an ophthalmologist if eye pain persists or if there is significant corneal injury.

## SODIUM HYPOCHLORITE (BLEACH) POISONING

Sodium hypochlorite is a chemical commonly found in bleach, water purifiers, and cleaning products**.** Sodium hypochlorite is a green/yellow liquid with the characteristic smell of chlorine and it is commonly known as bleach (berkina). Sodium hypochlorite is used as a disinfectant and as a bleaching agent. It is also used in the disinfectant process of drinking-water and in swimming pools. Household bleach usually contains approximately 5 % sodium hypochlorite, although some may contain up to 10 %. Chlorine is heavier-than-air, yellowish-green gas with an irritating odor. Hypochlorite is an aqueous solution produced by the reaction of chlorine gas with water. The addition of acid to hypochlorite solution may release chlorine gas. The addition of ammonia to hypochlorite solution may release chloramine, a gas with properties similar to those of chlorine.

- **Mechanism of toxicity:** if sodium hypochlorite is mixed with acidic products, chlorine gas is produced. Chlorine gas produces a corrosive effect on contact with moist tissues such as the eyes and upper respiratory tract.
- **Clinical presentation**
  - Airways and lungs: fumes causes coughing, burn in (Eyes, ears, nose), pain in the mouth, and pain in the throat, chest tightness, coughing and difficulty of breathing. In more severe cases increased breathing rate, wheezing, swelling of the airways and respiratory failure may occur, the onset of which may take up to 36 h.
  - Heart and blood vessels: rarely cardiovascular collapse and Shock.

- Nervous system: delirium, coma
- Skin: irritation of the exposed area, burns, blistering
- Stomach and intestines: stomach or abdominal pain, vomiting
- Chloramine is less water-soluble and may produce more indolent or delayed irritation.

- **Toxic dose**
  - **Chlorine gas**: the recommended workplace limit for chlorine gas is 0.5 ppm (1.5 mg/$m^3$) as an 8 h time-weighted average. The short-term exposure limit is 1 ppm. The level considered immediately dangerous to life or health is 10 ppm.
  - **Aqueous solutions**: dilute aqueous hypochlorite solutions (3–5%) commonly found in homes rarely cause serious burns but are moderately irritating. However, more concentrated industrial cleaners (20% hypochlorite) are much more likely to cause serious corrosive injury.
- **Diagnosis:** based on a history. Other useful laboratory studies include, for ingestion, CBC, electrolytes, and chest and abdominal x-rays; for inhalation, arterial blood gases and pulse oximetry.
- **Treatment**
  - Emergency and supportive measures
  - ✓ **Inhalation of chlorine gas:** remove immediately from exposure, immediately give humidified supplemental oxygen. Observe carefully for signs of progressive upper-airway obstruction, and intubate the trachea if necessary. Use bronchodilators for wheezing and treat non-cardiogenic pulmonary edema if it occurs.
  - ✓ **Ingestion of hypochlorite solution:** if a solution of 10% or greater has been ingested, or if there are any symptoms of corrosive injury (dysphagia, drooling, or pain), flexible endoscopy is recommended to evaluate for serious esophageal or gastric injury. Obtain chest and abdominal x-rays to look for mediastinal or intra-abdominal air, which suggests perforation.
  - **Decontamination**: for oral exposures, emesis and activated charcoal are contraindicated. Instead, immediately give water by mouth. Do not induce vomiting. Do not use activated charcoal; it may obscure the endoscopes' view.

- **Skin and eyes**: remove contaminated clothing, and flush exposed skin immediately with copious water. Irrigate exposed eyes with water or saline. Bathing with mild shampoo and thorough rinsing for significant dermal exposures is recommended.

## DETTOL POISONING

Dettol is a commonly available house-hold disinfectant. It contains Isopropyl alcohol (12%), Chlorxylenol (4.8%), and Pine oil (9%). Pine oil is made of secondary and tertiary terpene alcohols. As a result, it can cause CNS depression. The action is probably additive to the depressant action of Chlorxylenol. Similar to Chlorxylenol, Pine oil can cause renal failure and hepatitis. Iso-propyl alcohol can also cause CNS depression.

- **Mechanism of toxicity:** it causes CNS depression, corrosion of oral mucosa and gastrointestinal tract, laryngeal edema, upper airway obstruction, nephrotoxicity, hepatitis and cardiac arrhythmias. However the main risk of poisoning is aspiration with subsequent development of acute respiratory distress syndrome (ARDS), pneumonia and sudden cardio-respiratory arrest. Micro-aspiration has been hypothesized to be the reason for delayed upper airway obstruction that may occur in totally asymptomatic patients up to 48 h after admission.
- **Clinical presentation:** CNS drowsiness, upper GI hemorrhage, air way obstruction, bronchospasm, pneumonia, adult respiratory distress and sudden cardio- respiratory arrest, renal toxicity and hepatotoxicity.
- **Treatment:** the mainstay of dettol poisoning is supportive management along with close observation in hospital for stridor. Emesis and gastric lavage should not normally be attempted. The only indication for gastric lavage in the acute setting is a patient who has consumed other poison along with Dettol. Patient should be started on IV fluids with regular monitoring of electrolytes. Adolescents and adults who have consumed more than 200 to 300 ml and children who have consumed lesser amounts should be kept nil per oral (NPO) and watched carefully for signs and symptoms of nephrotoxicity and CNS depression. In case of severe poisoning or any evidence of hematuria or azotemia, forced alkaline diuresis should be attempted to aid in excretion of the poisons. Exchange transfusion, and early dialysis for isopropyl alcohol can be attempted in rare patients who are deteriorating steadily despite adequate supportive measures. Even patients who arrive comatose to the ED frequently

demonstrate a rapid and complete recovery. It is, however, important to remember that even patients who recover completely should be monitored closely in hospital for stridor for a minimum of 48 hours after admission.

## HYDROGEN PEROXIDE POISONING

Hydrogen peroxide is an antiseptic applied to living tissue to kill or prevent the growth of microorganisms and is a liquid commonly used to fight germs. Hydrogen peroxide poisoning occurs when large amounts of the liquid come in contact with the lungs or eyes.

- **Mechanism of toxicity:** it is a strong oxidizing agent, but it is very unstable and readily breaks down to oxygen and water. Generation of oxygen gas in closed body cavities can potentially cause mechanical distention resulting in gastric or intestinal perforation, as well as venous or arterial gas embolism. Direct contact with concentrated solutions can produce severe eye damage and skin irritation, including erythema and vesicle formation. Vapors are irritating to eyes, skin, mucous membranes, and respiratory tract.
- **Toxic dose:** hydrogen peroxide for household use is available in 3–5% solutions and it causes only mild throat and gastric irritation with ingestion of less than 1 oz. Concentrations above 10% are found in some hair-bleaching solutions and are potentially corrosive. Normally, the chemical is prepared in three different preparations (Hydrogen peroxide, Hair bleach and some contact lens disinfectants). Household hydrogen peroxide has a 3% concentration. Hair bleaches usually have a concentration of greater than 6%. Some industrial-strength solutions contain up to 90% hydrogen peroxide. Most reported deaths have been associated with ingestion of undiluted 35% hydrogen peroxide, which is often known as “Food grade”.
- **Clinical manifestations:** cause gastric distention and, rarely, perforation, severe corrosive injury and air emboli have been reported with the concentrated forms and may be caused by the entry of gas through damaged gastric mucosa or gas production within the venous or arterial circulation. Yet, most ingestion is benign, and mild irritation is self-limited. Abdominal pain and cramping, breathing difficulty (if large concentrations were swallowed) body aches, burns in the mouth and throat , chest pain, eye burns, seizures (rare), and vomiting (sometimes with blood) could occur.

- **Diagnosis:** based on history of exposure and with mild gastrointestinal upset or frank corrosive injury. Other useful laboratory studies include electrolytes, glucose and upright chest x-ray (for suspected gastric perforation).
- **Treatment**
  - Emergency and supportive measures: in patients, who have ingested concentrated solutions, monitor the airway for swelling and intubate if necessary. Consult a gastroenterologist for possible endoscopy. Consider hyperbaric oxygen treatment for gas emboli associated with concentrated peroxide ingestion.
  - **Decontamination:** dilute immediately with water or milk, do not induce vomiting because of the risk of corrosive injury. Perform gastric lavage cautiously. Activated charcoal and cathartics are not effective.
  - Eyes and skin: irrigate the eyes and skin with copious amounts of tepid water. Remove contaminated clothing.

## CARBON MONOXIDE POISONING

Carbon monoxide (CO) is an odorless, colorless, tasteless, and non-irritating gas produced by the incomplete combustion of any carbon-containing material (e.g., wood, coal). Common sources of human exposure include smoke inhalation in fires, faulty or poorly ventilated charcoal, kerosene or gas.

- **Mechanism of toxicity:** toxicity results from cellular hypoxia and ischemia.
  - CO binds to hemoglobin with an affinity 200 to 300 times greater than that of oxygen resulting in reduced oxyhemoglobin saturation and decreased blood oxygen-carrying capacity.
  - CO may also directly inhibit cytochrome oxidase, further disrupting cellular function.
  - Fetal hemoglobin is more sensitive to binding of CO, and fetal or neonatal levels may be higher than maternal levels.
  - Tissue hypoxia increases cerebral blood flow, cerebrospinal fluid pressure, and cerebral capillary permeability, which predispose the patient to cerebral edema.
  - CO also binds to myoglobin, which may lead to development of cardiac ischemia and/or dysrhythmias.
- **Clinical Manifestations:** high index of clinical suspicion is important

- ***Acute carbon monoxide poisoning:***
- ✓ Mild levels: headache, dizziness, weakness, nausea, malaise
- ✓ Moderate: confusion, lethargy, syncope, nystagmus, ataxia
- ✓ Sever: coma, convulsions, pulmonary edema, myocardial infarction, cardiac arrest
- ***Sub-acute clinical squeal of CO poisoning:*** persistent neurologic and myocardial dysfunction; ischemic skin; muscle and neural tissue injury resulting in bullous changes; rhabidomyolysis; peripheral neuropathy; and aspiration Pneumonitis
- CO-induced delayed neuropsychological squeal (DNS): neurobehavioral changes that occur following exposure to carboxyhemoglobin. Onset occurs between several days and several weeks or even months following exposure. Changes could include decreased cognitive function, personality changes, dementia, Parkinson and decerebrate rigidity
- Exposure during pregnancy may result in fetal death.

- **Diagnosis:** history and blood levels of carboxyhemoglobin may help document the diagnosis and may aid prognosis. Other laboratory studies include electrolytes, glucose, BUN and creatinine.
- **Treatment**

Most important measure is to remove the victim from the source environment. Rescuers exposed to high exposure CO should wear protective self-contained breathing apparatus. Maintain an open airway and assist ventilation if necessary. If smoke inhalation has also occurred, consider early intubation before airway edema. Administer oxygen in the highest possible concentration (100%). Breathing 100% oxygen speeds the elimination of CO from hemoglobin to approximately 1 h, compared with 6 h in room air. Use a tight-fitting mask and high-flow oxygen with a reservoir (non-rebreather) or administer the oxygen by endotracheal tube. Treat until the carboxyhemoglobin level is less than 5%. Treat coma and seizures if they occur.

Continuously monitor the ECG for several hours after exposure. Because smoke often contains other toxic gases, hence, consider the possibility of cyanide poisoning, methemoglobinemia, and irritant gas injury. The possibility of coexistent cyanide poisoning should be considered (especially where nitrogen-containing synthetic materials have burned) who have a persistent metabolic acidosis in the context of normal carboxyhemoglobin and methemoglobin. Cyanide has high fatality but a short half-life (approximately 1 h).

Provide 100% oxygen by tight-fitting mask or via endotracheal tube. Consider **hyperbaric oxygen therapy,** if the patient has serious poisoning and the patient can be treated within 6 h of the exposure.

**Hyperbaric oxygen usually three hyperbaric oxygen** is given under 2–3 atm of pressure and can enhance elimination of CO (half-life reduced to 20–30 min). It may be useful in patients with severe intoxication who do not respond rapidly to oxygen at atmospheric pressure, or for pregnant women or newborns, when there is ready access to a chamber.

## MUSHROOM POISONING

Mushroom is a great source of nutrition except for the fact that some are highly toxic. It is one of the common causes of plant poisoning. The majority of toxic mushrooms cause mild to moderate self-limited gastroenteritis. A few species may cause severe or even fatal reactions even though about 100 types of mushrooms are toxic.

There are many types of toxic mushrooms, of which the toxicity mechanism are nearly similar. It contains different toxic agents (i.e.muscarine, amatoxins, monomethylhydralizine, coprine, ibotenic acid to name some).

- **Mechanism of toxicity**
  - Majority of the toxic incidents are caused by gastrointestinal irritants that produce vomiting and diarrhea shortly after ingestion.
  - Amatoxins are thought to act by inhibiting cellular protein synthesis by interfering with RNA polymerase.A bsorption of amatoxins (and phalloidins) by intestinal cells causes' cell death and sloughing after a delay of 8–12 h. Absorption by the liver and kidneys results in severe hepatic necrosis and renal failure.
  - Two main groups of Mushrooms can be characterized on the basis of the time interval between ingestion and symptom onset: those with an immediate onset of symptoms within 6 h of ingestion usually confer a benign prognosis, and those with delayed onset.
  - ✓ Early-onset Mushrooms: cause muscarinic effects, usually within 15 min, such as sweating, salivation, colic, and pulmonary edema. Other early-onset mushrooms cause anticholinergic effects, including drowsiness, followed by mania and hallucinations. Another subgroup of early-onset mushrooms produces a severe gastroenteritis syndrome. Hallucinogenic mushrooms such as those containing psilocybin make up another class of mushrooms with early-onset symptoms. Finally, some mushrooms precipitate a

disulfiram-like reaction if they are co ingested with alcohol. The muscarinic effect syndrome responds to atropine therapy.

- ✓ The second, more important, categories of mushrooms that are responsible for 90% of mushroom-related deaths are those associated with onset of symptoms that occur more than 6 h after ingestion. The most important members of this group are those mushrooms that belong to the *Amanita phalloides* species. With these mushrooms, after a latent period of many hours, GI upset appears. Approximately 24 h after ingestion, hepatic dysfunction appears which may progress to fulminant hepatic failure. Without liver transplantation, such patients generally die.

- **Clinical presentation:** symptoms are characteristically delayed 8–12 h or more after ingestion. Early occurring death (1-2 days) usually results from massive fluid loss, while death occurring later usually results from hepatic failure.
  - **Gastroenteritis**: vomiting is accompanied by severe abdominal cramps and explosive watery diarrhea. Severe fluid losses and electrolyte imbalance can occur rapidly, and some patients die of shock within 24 h.
  - **Hepatic failure.** Liver injury may be apparent within 24–36 hours, with rapidly rising transaminase levels. Fulminant hepatic failure may follow, with jaundice, encephalopathy, and death.
- **Diagnosis**: usually done based on history of wild-mushroom ingestion
  - A radioimmunoassay has been developed for amatoxins but is not widely available.
  - A qualitative test (the Meixner test) may determine the presence of amatoxins in mushroom specimens. A single drop of concentrated hydrochloric acid is added to dried juice from the mushroom cap that has been dripped onto newspaper or other unrefined paper; a blue color suggests the presence of amatoxins. **Caution**: this test has unknown reliability and can be misinterpreted or poorly performed; it should not be used to determine the edibility of mushroom specimens.
  - **Other useful laboratory studies** include: electrolytes, glucose, BUN, creatinine, liver transaminases, bilirubin, and PT.
- **Treatment:** the mortality rate may be higher than 60% if the patient is not treated for severe fluid losses,

- Emergency measures: Maintain an open airway; supplement oxygen and ventilation if necessary. Treat fluid and electrolyte losses aggressively, because massive fluid losses may cause circulatory collapse. If renal failure develops, dialysis may be necessary. Early use of repetitive activated charcoal, which appears to interrupt enterohepatic recirculation of the toxin, is advisable. But multiple-doses of activated charcoal and vigorous attention to supportive care remain the standard. Provide vigorous supportive care for hepatic failure. Repeat-dose activated charcoal may trap small quantities of amatoxin undergoing enterohepatic recirculation. Activated charcoal plays a very important role in decontamination of patients with Amanta poisioning and is indicated for all patients. CNS excitement and hallucinations are treated with sdiazepam, 0.1 mg/kg iv, or phenobarbital, 30 mg iv. Muscarinic symptoms are treated with Atropine but rarely used as symptoms are usaually self limiting and respond to supportive treatment.

## HYDROCARBONS

Hydrocarbons, or petroleum distillates, are widely used in the petroleum, plastic, agricultural, and chemical industries as solvents, degreasers, fuels, and pesticides. Examples—kerosene, turpentine substitutes, petrol, and benzene.

- **Mechanism of toxicity:** toxicity from hydrocarbons may be caused by direct injury from pulmonary aspiration or systemic intoxication after ingestion, inhalation, or skin absorption. Many hydrocarbons are also irritating to the eyes and skin. The feature that these agents have in common is a low viscosity and surface tension that permits them to spread freely over large surface areas, such as the lungs, when ingested. This property leads to a necrotizing, potentially fatal chemical pneumonitis when these compounds are aspirated. The high volatility of these substances is responsible for alterations in mental status, including narcosis, inebriation, and frank coma. In addition to these toxicities, the solvents possess additional toxicities, including the risk of bone marrow injury (in the case of benzene). Aliphatic hydrocarbons and simple petroleum distillates such as lighter fluid, kerosene, furniture polish, and gasoline are poorly absorbed from the gastrointestinal tract and do not pose a significant risk of systemic toxicity after ingestion, as long as they are not aspirated. In contrast, many aromatic and halogenated hydrocarbons, alcohols, ethers, ketones, and other substituted or complex hydrocarbons are capable of causing serious systemic toxicity, such as coma, seizures, and cardiac arrhythmias. Inhalation of any hydrocarbon vapors in an

enclosed space may cause intoxication as a result of systemic absorption or by displacing oxygen from the atmosphere. Dermal absorption can be significant for some agents but is insignificant for most of the simple, aliphatic compounds.

- **Toxic dose:** the toxic dose is highly variable depending on the agent involved and whether it is aspirated, ingested, or inhaled. Pulmonary aspiration of as little as a few milliliters may produce chemical pneumonitis. Ingestion of as little as 10–20 mL of some systemic toxins, such as camphor or carbon tetrachloride, may cause serious or fatal poisoning.
- **Clinical presentation:** if pulmonary aspiration has occurred, there is usually immediate onset of coughing, gagging, or choking. This may progress within a few hours' to tachypnea, wheezing, and severe chemical pneumonitis. Death may ensue from secondary bacterial infection and other respiratory complications. Ingestion often causes abrupt nausea and vomiting, occasionally with hemorrhagic gastroenteritis. Some compounds may be absorbed and produce systemic toxicity.Systemic toxicitycaused by ingestion of a toxic hydrocarbon or inhalation of any hydrocarbon gas or vapor is highly variable depending on the compound but usually includes confusion, ataxia, lethargy, and headache. With significant exposure, syncope, coma, and respiratory arrest may occur. Cardiac arrhythmias may occur owing to myocardial sensitization. This is most commonly reported with chlorinated and fluorinated compounds and aromatic derivatives. With many agents, hepatic and renal injury may occur. Skin or eye contact may cause local irritation, burns, or corneal injury. Chronic exposure often causes a defatting dermatitis resulting from removal of oils from the skin. Some agents are absorbed through the skin.
- **Diagnosis.**
  - **Aspiration pneumonitis:** diagnosis is based on history of exposure and the presence of respiratory symptoms such as coughing, choking, and wheezing. If these symptoms are not present within 6 h of exposure, it is very unlikely that chemical pneumonitis will occur. Chest x-ray and arterial blood gases or oximetry may assist in the diagnosis of chemical pneumonitis.
  - **Systemic intoxication:** diagnosis is based on history of ingestion or inhalation, accompanied by the appropriate systemic clinical manifestations.
  - **Specific levels:** are generally not available or useful.

- **Other useful laboratory studies:** include arterial blood gases or oximetry and chest x-ray for suspected aspiration pneumonitis; and electrolytes, glucose, BUN, creatinine, liver transaminases, and ECG monitoring for suspected significant inhalation or ingestion of a toxic compound. Aspiration of the product may also occur at the time of the initial swallowing. If the patient has any cough or respiratory symptoms upon arrival to the ED, a chest radiograph should be obtained immediately. Clinical findings such as chest retractions, grunting, cough, and fever may occur as soon as 30 min after aspiration or may be delayed for several hours. Lung radiographic changes usually occur within 2-8 h, peaking in 48-72 h. Neumatoceles and pleural effusions may occur.Other organ systems, especially the liver, central nervous system, and heart, may suffer serious injury. Cardiac dysrhythmias may occur and may be exacerbated by hypoxia and acid-base or electrolyte disturbances.

- **Treatment**
  - **Emergency and supportive measures:** provide basic supportive care for all symptomatic patients, whether from aspiration, ingestion, or inhalation. Because most hydrocarbons cause clinical toxicity only when aspirated, the mainstay of treatment is to leave ingested compounds in the gut (when possible) and to prevent emesis or reflux. Gastric emptying is generally reserved only for those compounds with the potential for systemic toxic effects. Gastric emptying is nearly always contraindicated because the risk of aspiration is greater than any systemic toxicity. Treatment is generally supportive, consisting of oxygen, fluids, and ventilatory support as necessary. The child who has no symptoms and normal chest radiograph findings should be observed for 6-8 h to ensure safe discharge. Certain hydrocarbons have more inherent systemic toxicity. The pneumonic **CHAMP** refers collectively to the following hydrocarbons: **c**amphor, **h**alogenated carbons, **a**romatic hydrocarbons, and those associated with **m**etals and **p**esticides. Patients who ingest these compounds in volumes >30 mL, such as might occur with intentional overdose, may benefit from gastric emptying. This is still a high-risk procedure that can result in further aspiration. If a cuffed endotracheal tube can be placed without inducing vomiting, this procedure should be considered, especially in the presence of altered mental status. Treatment of each case should be considered individually, with guidance from a poison control center. ***Antibiotics should not be used***

***prophylactically but should be reserved for specific infections if they develop. The use of corticosteroids in the treatment of aspiration from hydrocarbons has been associated with increased morbidity and is not recommended. In the event of hypotension or bronchospasm, epinephrine is contraindicated because hydrocarbons are known to cause ventricular irritability and predispose to fibrillation, an effect that is exacerbated by catecholamines.*** Surfactants have been used in some cases to treat Acute Lung Injury from hydrocarbon poisioning.

- **Other substances** that are particularly toxic and cause significant lung injury when aspirated or inhaled include baby powder, chlorine, shellac, beryllium, and mercury vapors. Repeated exposure to low concentrations of these agents can lead to chronic lung disease, such as interstitial pneumonitis and granuloma formation. Corticosteroids may help reduce fibrosis development and improve pulmonary function, although the evidence for this benefit is limited.
- **Specific drugs and antidotes**

✓ There is no specific antidote for general hydrocarbon aspiration pneumonia; corticosteroids are of no proven value.

✓ Specific drugs or antidotes may be available for systemic toxicity of some hydrocarbons (e.g., acetylcysteine for carbon tetrachloride and methylene blue for methemoglobin formers) or their solutes (e.g., chelation therapy for leaded gasoline and antidotes for pesticides, etc).

- **Decontamination**

✓ **Inhalation:** move the victim to fresh air and administer oxygen if available.

✓ **Skin and eyes:** remove contaminated clothing and wash exposed skin with water and soap. Irrigate exposed eyes with copious tepid water or saline and perform fluorescein examination for corneal injury.

✓ **Ingestion:** for agents with no known systemic toxicity, gut decontamination is neither necessary nor desirable because any gut-emptying procedure may increase the risk of aspiration.

✓ **For systemic toxins**

❖ **Prehospital:** administer activated charcoal if available. Do ***not*** induce vomiting, because systemic complications such as seizures and coma may occur rapidly or abruptly. Risks

of aspiration far outweigh any of its benefits. Activated charcoal does not adsorb hydrocarbons and should not be given.

- ❖ **Hospital: DO NOT** Administer activated charcoal. Consider gastric lavage for large recent ingestions.
- ➢ **Enhanced elimination:** there is no known role for any of these procedures.
- ➢ **Note:** because there is a gradual evolution of abnormal radiographs, an initially negative chest radiograph should be repeated at 4 to 6 h after ingestion. All patients with abnormal chest radiographs or persistent respiratory symptoms after 4 to 6 h of ED observation warrant further medical observation. Patients who are asymptomatic after this period of observation may be discharged. Because pneumonitis occasionally appears 12 to 24 h after exposure, detailed instructions should be provided for warning signs of respiratory dysfunction. Consider propranolol, esmolol, or lidocaine for ventricular dysrhythmias.

## ORGANOPHOSPHATES AND CARBAMATES

Organophosphates and carbamates, also known generally as cholinesterase inhibitors, are widely used pesticides that may cause poisonings after accidental or suicidal exposure. Poisonings are particularly common in rural areas where more potent agents are widely available. Household insect sprays often contain low-potency organophosphates or carbamates. These compounds are found in agricultural insecticides and home use. Compounds of this class can be absorbed by inhalation, ingestion, and skin penetration. Examples include organophosphorus – Malathion, parathion, tetraethyl pyrophosphate (TEPP), mevinphos (Phosdrin); and carbamates- methiocarb, carbaryl.

- **Mechanism of toxicity.**
  - ➢ Organophosphate derivatives inhibit the enzyme acetylcholinesterase, allowing accumulation of excessive acetylcholine at cholinergic receptors. Permanent damage to the acetylcholinesterase enzyme (“aging”) may occur after a variable delay unless antidotal treatment with an enzyme reactivator is given. Afterwards, a period of weeks to months is required to regenerate inactivated enzymes.
  - ➢ Carbamates also inhibit acetylcholintesterase and produce similar clinical effects. However, binding to the enzyme is reversible and toxicity is usually brief and self-limited, typically allowing reactivation of acetylcholinesterase within 24 h.

- **Pharmacokinetics:** organophosphates and carbamates are well absorbed by inhalation and ingestion and through the skin. Some organophosphates may lead to delayed and persistent toxicity for several days after exposure.
- **Toxic dose:** there is a wide spectrum of relative potency of the organophosphates and carbamates. The degree of intoxication is also affected by the rate of exposure (acute versus chronic), the ongoing metabolic degradation and elimination of the agent, and for organophosphates, the rate of metabolism to their more toxic "-oxon" derivatives.
- **Clinical presentation:** four clinical syndromes are described following organophosphate exposure: acute poisoning, intermediate syndrome, chronic toxicity, and organophosphate induced delayed neuropathy.
  - Signs and symptoms of **acute organophosphate poisoning** usually occur within 1–2 h of exposure but may be delayed up to several hours, especially after skin exposure. Clinical manifestations may be classified intoperipheral muscarinic and nicotinic as well as CNS effects. In addition, chemical pneumonitis may occur if a product containing a hydrocarbon solvent is aspirated into the lungs. Muscarinic manifestations include vomiting, diarrhea, abdominal cramping, bronchospasm, miosis, bradycardia, and excessive salivation and sweating. Severe diaphoresis can actually lead to dehydration with systemic hypovolemia, resulting in shock. Nicotinic effects include muscle fasciculations, tremor, and weakness. Death is usually caused by respiratory muscle paralysis. Blood pressure and pulse rate may be increased because of nicotinic effects or decreased because of muscarinic effects. Central nervous system poisoning may cause agitation, seizures, and coma. Some organophosphates may cause a delayed, often permanent peripheral neuropathy.
  - An **"intermediate syndrome**" has also been described, characterized by recurrent muscle weakness occurring within several days of the exposure. It may be associated with inadequate pralidoxime therapy. Severe intoxications may also cause a toxic psychosis that resembles alcoholism. An intermediate syndrome may occur 1 to 5 days after an organophosphate exposure, reported in up to 40% of patients following ingestion. Clinical features include paralysis of neck flexor muscles, muscles innervated by the cranial nerves, proximal limb muscles, and respiratory muscles; respiratory support may be needed. Symptoms or signs of cholinergic excess are absent in this syndrome.

Electromyography may assist in making the diagnosis. Aggressive, early antidote therapy and supportive measures may prevent or ameliorate the severity of this syndrome. Symptoms usually resolve within 7 days. Treatment options like Oximes are controversial till date.

- **Chronic toxicity** is seen primarily in agricultural workers with daily exposure, manifesting as symmetrical sensorimotor axonopathy. This mixed sensorimotor syndrome may begin with leg cramps and progress to weakness and paralysis, mimicking features of the Guillain-Barré syndrome
- **Organophosphate-induced delayed neuropathy** is characterized by cognitive dysfunction, impaired memory, mood changes, autonomic dysfunction, peripheral neuropathy, and extrapyramidal signs. Chronic fatigue syndrome and multiple chemical sensitivities have been reported in some patients, predominantly female, after exposure to very low doses of organophosphate insecticides. Children are at greater risk of toxicity when exposed due to smaller body size and lower baseline levels of cholinesterase activity.

- **Diagnosis:** is based on history of exposure and the presence of characteristic peripheral and central manifestations of acetylcholine excess. There may be a solvent odor, and some organophosphates have a strong garlicky odor.
  - Specific levels measurement if available, applicable and feasible
  - Other useful laboratory studies include electrolytes, glucose, BUN, creatinine, liver transaminases, arterial blood gases or oximetry, ECG monitoring, and chest x-ray (if pulmonary edema or aspiration of hydrocarbon solvent is suspected).
- **Treatment.**
  - **Emergency and supportive measures: *caution***: rescuers and health care providers must take measures to prevent direct contact with the skin or clothing of contaminated victims, because secondary contamination and serious illness may result, especially with potent pesticides and nerve agents.
    - ✓ ABC of life: pay careful attention to respiratory muscle weakness; sudden respiratory arrest may occur. If intubation is required, one should be aware of potential interactions between neuromuscular blockers and cholinesterase inhibitors.
    - ✓ Administer supplemental oxygen.

- ✓ Monitor patients for hydrocarbon induced pneumonitis, treat seizures, and coma if they occur.
- ✓ Observe patients for at least 6–8 h to rule out delayed-onset symptoms resulting from skin absorption.

- ➢ **Decontamination: Note**: the management of a patient who has ingested organophosphates must always include safeguards against exposure for the persons who treat the patient because the organophosphates are readily absorbed through the skin and mucous membranes. If there is heavy liquid contamination with a solvent, clothing removal and victim decontamination should be carried out outdoors or in a room with high-flow ventilation.
  - ✓ Skin: remove all contaminated clothing and wash exposed areas with soap and water, including the hair and under the nails. Irrigate exposed eyes with water or saline.
  - ✓ Ingestion
    - ❖ Prehospital: administer activated charcoal, if available. Do not induce vomiting because of the risk of abrupt onset of toxicity.
    - ❖ Hospital: administer activated charcoal (cathartics are not necessary if the patient already has diarrhea). Perform gastric lavage for large recent ingestions.
- ➢ **Enhanced elimination:** dialysis and hemoperfusion are not generally indicated because of the large Vd of organophosphates and effectiveness of the specific therapy described above. Repeat-dose activated charcoal is theoretically applicable to aldicarb poisoning, because the agent undergoes significant enterohepatic recirculation.
- ➢ **Specific drugs and antidotes:** include the antimuscarinic agent atropine and the enzyme reactivator pralidoxime.
- ✓ **ATROPINE**
  - ❖ Atropine sulfate given in a dose of 0.05 to 0.1 mg per kg to children and 2 to 5 mg for adolescents and adults.
  - ❖ Repeated every 10 to 30 minutes till full atropinization.
  - ❖ Atropinazation is indicated by an end point of clearing bronchial secretions and pulmonary rales.
  - ❖ Therapy is continued until all absorbed organophosphate has been metabolized and may require 2 mg to more than 2,000 mg of atropine.

- ❖ The indication to continuewith atropine is persistent wheezing or bronchorrhea.

**Note**: Atropine will reverse muscarinic but not nicotinic effects.

- ❖ After atropinization has been instituted, severe poisonings should be treated with the addition of pralidoxime.
- ❖ It acts to regenerate the enzyme activity at all affected sites, however, it does not reactivate plasma cholinesterase.
- ❖ A dose of 25 to 50 mg per kg should be administered in 100 mL of saline by infusion over approximately 30 minutes; adults may receive 1 to 2 g by IV.
- ❖ The end point should be persistent relief of neurologic and cholinergic signs.
- ❖ Pralidoxime is not generally recommended for carbamate intoxication, because in such cases the cholinesterase inhibition is spontaneously reversible and short-lived.

**Note:** organophosphates are usually dissolved in hydrocarbon bases. Thus, the clinician should be prepared to treat hydrocarbon induced pneumonitis if it develops. Also, bronchopneumonia that complicates pulmonary edema has been observed in acute poisonings. Because organophosphates cause elevated levels of acetylcholine in the plasma, compounds that affect the uptake of acetylcholine and/or its release should be avoided in the management of these patients. Specifically, aminophylline, succinylcholine and phenothiazines are contraindicated.

## HERBICIDES

Chlorophenoxy compounds have been widely used as herbicides. Agent Orange was a mixture of the chlorophenoxy herbicides 2,4-D (dichlorophenoxyacetic acid) and 2,4,5-T (trichlorophenoxyacetic acid) that also contained small amounts of the highly toxic contaminant TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) derived from the process of manufacturing 2,4,5-T. Commercially available 2,4-D does not contain TCDD. Concentrated formulations of 2,4-D are likely to contain petroleum solvents; while these are considered "inert" ingredients because they are not pesticides, they may have their own innate toxicity.

- **Mechanism of toxicity:** in plants, the compounds act as growth hormone stimulators. Their mechanism of toxicity in animals is not known. In animal studies, widespread muscle damage occurs, and the cause of death is usually ventricular fibrillation. Massive rhabdomyolysis has been described in human cases.

- **Toxic dose:** the minimum toxic dose of 2,4-D in humans is 3–4 g or 40–50 mg/kg, and death has occurred after adult ingestion of 6.5 g. Less than 6% of 2,4-D applied to the skin is absorbed systemically, although dermal exposure may produce skin irritation.
- **Clinical presentation:** tachycardia, muscle weakness, and muscle spasms occur shortly after ingestion and may progress to profound muscle weakness and coma. Massive rhabdomyolysis, metabolic acidosis, and severe and intractable hypotension have been reported, resulting in death within 24 h. Hepatitis and renal injury may occur.
- **Diagnosis:** depends on history of exposure and the presence of muscle weakness and elevated serum CPK.
  - **Specific levels** of urinary 2,4-D can be measured but may not be available in a timely enough fashion to be of help in establishing the diagnosis.
  - **Other useful laboratory studies** include electrolytes, glucose, BUN, creatinine, CPK, urinalysis (occult heme test positive in the presence of myoglobin), liver enzymes, 12-lead ECG and ECG monitoring.
- **Treatment.**
  - **Emergency and supportive measures**
  - ✓ Maintain an open airway and assist ventilation if necessary.
  - ✓ Treat coma, hypotension, and rhabdomyolysis if they occur.
  - ✓ Monitor the patient closely for at least 6–12 h after ingestion because of the potential for delayed onset of symptoms.
  - **Specific drugs and antidotes:** there is no specific antidote.
  - **Decontamination**
  - ✓ **Prehospital:** administer activated charcoal if available. Ipecac-induced vomiting may be useful for initial treatment at the scene (e.g., children at home) if it can be given within a few minutes of exposure.
  - ✓ **Hospital:** administer activated charcoal, and then perform gastric lavage. After lavage, give an additional dose of charcoal.
  - **Enhanced elimination:** there is no proven role for these procedures, although alkalinization of the urine may promote excretion of 2,4-D.

## RODENTICIDES

Rodenticides are commonly classified based on whether they are anticoagulants or non-anticoagulants. Ingestions are associated with high morbidity and mortality.

### 1. Non Anticoagulants

A number of non-anticoagulant rodenticides have been used throughout history. Common examples of such compounds include strychnine, Zinc or Aluminum phosphides, arsenic and elemental or yellow phosphorus. These compounds have been used in the past in barns to protect grains but some of them like the phosphides have been recently seen in suicidal and rarely homicidal ingestions.

### Zinc & Aluminum Phosphide toxicity

Belong to classes of rodenticides with extremely high inherent toxicity. These compounds when ingested combine with water and stomach acid to produce phosphine gas. This phosphine gas is responsible for the toxic effects seen. It results in cellular toxicity and necrosis to the GI tract, kidney, and liver when ingested and to the lungs if inhaled.

- **Clinical Features**: aluminium phosphate poisoning affects most organs and a variety of signs and symptoms appear in patients. These include **i**mmediate nausea, vomiting, epigastric pain, phosphorous or fishy breath, black vomitus, and GI irritation or ulceration; myocardial toxicity, shock, and acute lung injury; agitation, coma, seizures, hepatorenal injury, metabolic acidosis, hypocalcemia and tetany.
- **Management:** unfortunately the absence of a specific antidote results in very high mortality and the key to treatment lies in rapid decontamination and institution of resuscitative measures.
  - **Decontamination:** Gastric lavage is done with potassium permanganate or combination coconut oil and sodium bicarbonate**;**
  - **Supportive measures:** are all that can be offered and should be implemented as required by clinical developments. The most important factor for success is resuscitation of shock and institution of supportive measures as soon as possible. **Magnesium sulphate** is used for the treatment of arrhythmias. Routine supplementation of Magnesium has no proven benefit.

### 2. Anticoagulants

Warfarin-type anticoagulants were the first generation of anticoagulant rodenticides and distributed commonly. Examples include 4-hydroxy-coumarins brodifacoum, diphenacoum, couma furyl, and bromadoline. Most one-time warfarin rodenticide ingestions are insignificant accidental poisonings and do not cause any bleeding problems. Significant coagulopathy requires large amounts in a single exposure or a repetitive exposure over several days. Following a single large ingestion, onset of the anticoagulant effect takes place within 12 to 48 h. Warfarin`s biologic half-life is approximately 42 h.

- **Management:**
  - The diagnosis may not be readily apparent**.**
  - Depressed patients with an unexplained coagulopathy and/or bleeding should raise suspicion of super warfarin poisoning.
  - Monitor INR levels (baseline and repeat 24 and 48 hours after ingestion.)
  - Gastric lavage is indicated for early presentations, and activated charcoal should be administered.
  - If the INR is elevated but there is no active hemorrhage, oral vitamin K is recommended.
  - Because of the extended half-life of the anticoagulant, prolonged therapy with high doses of vitamin K is required to maintain hemostasis.

## SNAKEBITE

Of the 14 families of snakes, 5 are poisonous. Clinically significant morbidity occurs in less than 60%, and only a few deaths are reported. In children, snakebite should be considered in any severe pain or swelling of a limb or in any unexplained illness presenting with bleeding or abnormal neurological signs.

- **Mechanism of toxicity:** snake venoms are complex mixtures of 50 or more components that function to immobilize, kill, and predigest prey. In human victims, these substances produce local “digestive” effects on tissues as well as hemotoxic, neurotoxic, and other systemic effects. The relative predominance of digestive, hemotoxoic, or neurotoxic venom components depends on the species of the snake and geographic variables.

- **Toxic dose:** the potency of the venom and the amount of venom injected vary considerably. About 20% of all snake strikes are "dry" bites in which there is no envenomation.
- **Clinical presentation.**
  - **Crotalidae:** fang marks may look like puncture wounds or lacerations, the latter resulting from a glancing blow by the snake or sudden movement by the victim. The fangs often penetrate only a few millimeters but occasionally enter deeper tissue spaces or veins.
  - ✓ **Local effects:** within minutes of envenomation, stinging, burning pain begins. Progressive swelling, erythema, petechiae, ecchymosis, and hemorrhagic blebs develop over the next several hours. The limb may swell to twice its normal size within the first few hours. Hypovolemic shock and local compartment syndrome may occur secondary to fluid and blood sequestration in injured areas.
  - ✓ **Systemic effects:** may include nausea and vomiting, weakness, muscle fasciculations, diaphoresis, perioral and peripheral parasthesias, a metallic taste, thrombocytopenia, and coagulopathy. Circulating vasodilatory compounds may contribute to hypotension. Pulmonary edema and cardiovascular collapse have been reported.
  - **Mojave rattlesnake** (*Crotalusscutulatus*) bites deserve special consideration and caution, because neurologic signs and symptoms of envenomation may be delayed and there is often little swelling or evidence of tissue damage. The onset of muscle weakness, ptosis, and respiratory arrest may occur several hours after envenomation. Facial and laryngeal edema have also been reported.
  - **Elapidae:** coral snake envenomation is rare because of the snake's small mouth and fangs. The snake must hold on and "chew" the extremity for several seconds or more to work its rear fangs into the skin.
  - ✓ **Local effects:** there is usually minimal swelling and inflammation around the fang marks. Local paresthesias may occur.
  - ✓ **Systemic effects.** Systemic symptoms usually occur within a few hours but may be delayed 12 hours or more. Nausea and vomiting, euphoria, confusion, diplopia, dysarthria, muscle fasciculations, generalized muscle weakness, and respiratory arrest may occur.
  - **Colubridae:** these small-mouthed rear-fanged snakes must also hang onto their victims and "chew" the venom into the skin before significant envenomation can occur.

- ✓ **Local effects:** there is usually little local reaction other than mild pain and paresthesias, although swelling of the extremity may occur.
- ✓ **Systemic effects:** the most serious effect of envenomation is systemic coagulopathy, which can be fatal.

- **Diagnosis:** correct diagnosis and treatment depend on proper identification of the offending snake.
  - ➢ ***Caution:*** Be careful not to handle a "dead" snake; accidental envenomation may still occur up to several hours after death.
  - ➢ **Other useful laboratory studies** include CBC, platelet count, and PT, CPK, and urine dipstick for occult blood (positive with free myoglobin or hemoglobin). For severe envenomations with frank bleeding, hemolysis, or anticipated bleeding problems obtain a blood type and screen early. If compromised respiratory function is suspected, closely monitor oximetry and arterial blood gases.
  - ➢ **In children:**
  - ✓ Diagnosis of envenoming: general signs include shock, vomiting and headache. Examine bite for signs such as local necrosis, bleeding or tender local lymph node enlargement. Specific signs depend on the venom and its effects. These include
  - ✓ Shock, local swelling that may gradually extend up the bitten limb; .
  - ✓ Bleeding: external from gums, wounds or sores; internal especially intracranial
  - ✓ Signs of neurotoxicity: respiratory difficulty or paralysis, ptosis, bulbar palsy (difficulty swallowing and talking), limb weakness.
  - ✓ Signs of muscle breakdown: muscle pains and black urine.
  - ✓ Check haemoglobin (where possible, blood clotting should be assessed).
- **Treatment.**
  - ➢ ***First aid:*** Assess and mange the ABCD of life includes treatment of shock/respiratory arrest. Splint the limb below the heart to reduce movement and absorption of venom. Apply a firm bandage to affected limb from fingers or toes to proximal of site of bite. Irrigation and dressing of the wound. Avoid cutting the wound or applying tourniquet. If any of the above signs, transport to hospital which has anti-venom as soon as possible. If snake has already been killed, take the snake or the photo with the child to hospital.

Paralysis of respiratory muscles can last for days and requires intubation and mechanical ventilation

- **Emergency and supportive measures:** regardless of the species, prepare for both local and systemic manifestations. Monitor patients closely for at least 6–24 h after bite.
  - ✓ **Local effects**
    - ❖ **Monitor local swelling** at least hourly with measurements of limb girth, the presence and extent of local ecchymosis, and assessment of circulation.
    - ❖ Obtain consultation with surgeon for management of serious wound complications.
    - ❖ Provide tetanus prophylaxis if needed.
    - ❖ Administer broad-spectrum antibiotics only if there are signs of infection.
  - ✓ **Systemic effects**
    - ❖ **Monitor the victim for respiratory muscle weakness.** Maintain an open airway and assist ventilation if necessary. Administer supplemental oxygen.
    - ❖ Treat bleeding complications with fresh-frozen plasma (and antivenin; see below). Treat hypotension with intravenous crystalloid fluids, and rhabdomyolysis with fluids and sodium bicarbonate.
- **Specific drugs and antidotes:** for patients with documented envenomation, be prepared to administer specific **antivenin**. Virtually all local and systemic manifestations of envenomation improve after antivenin administration. ***Caution:*** Life-threatening anaphylactic reactions may occur with antivenin administration, even after a negative skin test.
  - ✓ **Antivenom: i**f there are systemic signs or severe local signs (swelling of more than half of the limb or severe necrosis), give antivenom, if available. Prepare IM epinephrine (adrenaline) 10 µg/kg im and iv chlorpheniramine and be ready if allergic reaction occurs (see below). Promethazine im or iv can be given if allergic reaction occurs in antivenum administration. **Give monovalent antivenom** if the species of snake is known. Give polyvalent antivenom if the species is not known. Follow the directions given on the antivenom preparation. The dose for children is the same as for adults. Dilute the antivenom in 2–3 volumes of 0.9% saline and give intravenously over 1 hour. Give more slowly initially and monitor closely for

anaphylaxis or other serious adverse reactions. If itching/urticarial rash, restlessness, fever, cough or difficult breathing develops then stop antivenom and give epinephrine (adrenaline) 10 µg/kg (0.1ml/kg of 1 in 10,000) im. More anti-venom should be given after 6 h if there is recurrence of blood clotting disorder or after 1–2 h if the patient is continuing to bleed briskly or has deteriorating neurotoxic or cardiovascular signs. Blood transfusion should not be required if antivenom is given. Clotting function returns to normal only after clotting factors are produced by the liver. Response of abnormal neurological signs to antivenom is more variable and depends on type of venom. If there is no response to antivenom infusion this should be repeated. Anticholinesterases can reverse neurological signs in some species of snake (see standard textbooks for further details).

- ✓ **Surgical Management: s**eek surgical opinion if there is severe swelling in a limb, it is pulseless or painful or there is local necrosis. Surgical care will include: Excision of dead tissue from wound, Incision of fascial membranes to relieve pressure in limb compartments, if necessary Skin grafting, if extensive necrosis. Tracheostomy (or endotracheal intubation) if paralysis of muscles involved in swallowing occurs

- ➢ **Supportive care:** give fluids orally or by NG tube according to daily requirements. Keep a close record of fluid intake and output. Provide adequate pain relief. Elevate limb if swollen. Give anti-tetanus prophylaxis. Antibiotic treatment is not required unless there is tissue necrosis at wound site. Monitor very closely immediately after admission, then hourly for at least 24 h as envenoming can develop. Accidental Poisoning is common in children so suspecting and checking poisoning is useful in children with atypical presentations. Rather than trying to identify the poison, supportive treatment should take priority.
- ➢ **Decontamination.**
- ✓ Remain calm, remove the victim to at least 20 feet from the snake, wash the area with soap and water, and remove any constricting clothing or jewelry. Apply ice sparingly to the site (excessive ice application or immersion in ice water can lead to frostbite and aggravate tissue damage).
- ✓ Loosely splint or immobilize the extremity near heart level. *Do **not** apply a tourniquet*.

- ✓ Do ***not*** make cuts over the bite site. If performed within 15 minutes, **suction** over the fang marks (ie, with an extractor) may remove some venom but this should not delay transport to a hospital. Mouth suction of the wound is not advised.
- ➢ **Enhanced elimination:** dialysis, hemoperfusion, and charcoal administrationare not applicable.

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