Chapter 27
The Poisoned Patient

Choo Hock Tan and Ahmad Khaldun Ismail

Abstract Acute exposure to toxic or poisonous substances can be intentional or accidental. The onset of the toxic effect depends on the degree of absorption of the toxicant. The management of acute exposure to toxicants is generally supportive. Knowledge of the pharmacokinetics and pharmacodynamics of the offending agent is important. The use of pharmacological agents in treating poisoning is to manipulate the pharmacokinetic or pharmacodynamic profiles of the toxicant. These pharmacological agents will minimize the absorption and/or enhance the elimination of the toxicant from the body. Specific antidotes are used to alter the effects of certain known toxicants through neutralization and pharmacological antagonism. Having the ability to identify the effect of specific classes of substances on the body (toxidromes) will facilitate the selection of an appropriate management strategy to optimize the outcome.

Keywords Antagonism • Antidote • Toxicant • Toxin • Poison • Medical toxicology • Neutralization • Rebound phenomenon

Introduction

Medical toxicology is one of the four subspecialties of toxicology. It deals with human exposure to toxic substances. The origin of these toxic substances can be from animal, plant or synthetic materials. Human exposure to these toxoids and toxins can either be intentional (deliberate), unintentional (accidental) or fabricated (induced). Many toxins and toxoids have long been utilized as pesticides, herbicides, fertilizers, household cleaners, cosmetics, pharmaceutical and other useful

C.H. Tan, M.B.B.S., Ph.D. (✉)
Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
e-mail: tanch@um.edu.my

A.K. Ismail, MBBCh, BAO, BMedSc, Dr.Em.Med
Department of Emergency Medicine, Faculty of Medicine, UKM Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia

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products of daily use. Unfortunately, some of these substances have been used for intentional poisoning (of individuals, targeted groups of people or the general public), biological warfare and antipersonnel terrorism.

General Principles

The effects of poisoning or envenoming begin with the exposure to large enough amounts of xenobiotics (foreign, natural or man-made substances) to cause harm or damage to the body. These toxic substances enter the body through various routes such as oral (most common), intradermal, intravascular or inhalational. The rate of absorption predicts the onset of action, while the extent of absorption reflects the bioavailability and its pharmacological effect. Absorption rate, bioavailability and elimination of these toxicants are influenced by physical factors (molecular weight, blood flow, surface area, contact time) and chemical factors (water/lipid solubility, polarity, pH of the medium). The general approach to toxic exposures is to remove the patient from the substance and the substance from the patient as soon as and as completely as possible.

Approaches to Acute Poisoning

This involves various methods and pharmacological manipulation to alter the pharmacokinetics and pharmacodynamics of toxicants. Treatment should take place in tandem with but not be delayed by diagnostic, screening or laboratory investigations.

1. **Preventing further gastrointestinal (GI) absorption (Gastric decontamination)**
   (a) Emesis: Syrup ipecac (active compounds: emetine and cephaeline) act locally by irritating the gastric mucosa and centrally by stimulating the medullary chemoreceptor trigger zone to induce vomiting to reduce the poison load. Ipecac is only considered immediately post toxic ingestion due to the significant risk of aspiration especially in those with decreased level of consciousness.
   (b) Activated charcoal: This is the most frequently used agent for GI decontamination. The high degree of microporosity (>500 m^2 per g) of activated charcoal makes it an excellent adsorbing agent, binding to a wide selection of drugs and their metabolites. When administered early following toxic ingestion, it significantly reduces gastrointestinal absorption, enterohepatic circulation and enteroenteric circulation.
   (c) Cathartic: Cathartics enhance bowel transit. The indication is similar to activated charcoal and is often used with activated charcoal. Magnesium citrate, magnesium sulfate and sorbitol can decrease intestinal transit time

and absorption of the ingested xenobiotics. Severe diarrhea is a major adverse effect and requires careful monitoring of the hydration status. Magnesium salt-containing cathartics should be avoided in patients with renal failure, due to risk of magnesium toxicity.

(d) Gastrointestinal irrigation: Orogastric lavage with small amounts of warm fluid through an appropriately placed orogastric tube is only considered in alert patients presenting within 60 min of life threatening toxic ingestions. This procedure is limited to the irrigation of preparations small enough to pass through the orogastric tube, and substances that cause delay in gastric emptying, gastric outlet obstruction or concretion. Whole bowel irrigation using non-absorbable polyethylene glycol has a role in the toxic ingestion of petroleum products, iron, lithium, sustained-release-enteric-coated formulations or in patients who are "body packers" i.e. transporting illicit drugs in their bowel.

Clinical Correlation – Caution with Gastric Lavage and Removal from the Lower Gastrointestinal Tract

Inducing emesis or orogastric lavage involves manipulation of the upper gastrointestinal tract. This should be avoided in patients with decreased level of consciousness, seizure, absent gag reflex, and caustic ingestion. While activated charcoal works well for most drugs (aspirin, carbamazepine, digitalis, barbiturates, phenytoin etc.), it is not useful for substances like petroleum products, corrosives, mineral acids, ethanol/glycols, cyanide, boric acid, lithium, iron, and certainly must not be given with oral antidotes as it can bind and inactivate these agents. Manipulation of the lower intestinal tract (laxative use, bowel irrigation) is generally contraindicated in gut atony-related conditions and comatose or convulsive patients due to risk of gut perforation and aspiration.

2. **Increasing elimination (by manipulating urine pH, or by extracorporeal techniques)**

(a) Alkalinization of urine – weak acids like salicylates and barbiturates, ionize in alkaline urine resulting in an increase in their renal excretion (Fig. 27.1). Sodium bicarbonate is administered as IV bolus or infusion to maintain the urinary pH between 7.5 and 8.5. Continuous infusion is adjusted to clinical response or until serum pH is maintained between 7.50 and 7.55. This procedure is contraindicated in hypokalemia, and in those with renal insufficiency (not able to tolerate volume or sodium load).

(b) Acidification of urine – Basic drugs like amphetamines, quinine, ephedrine and flecainide, ionize in acidic urine and are excreted more readily. Urine acidifiers include ammonium chloride and vitamin C.

(c) Non-pharmacological approaches – peritoneal dialysis or hemodialysis can increase the elimination of salicylates, lithium, barbiturates, methanol, ethylene glycol and ethanol.

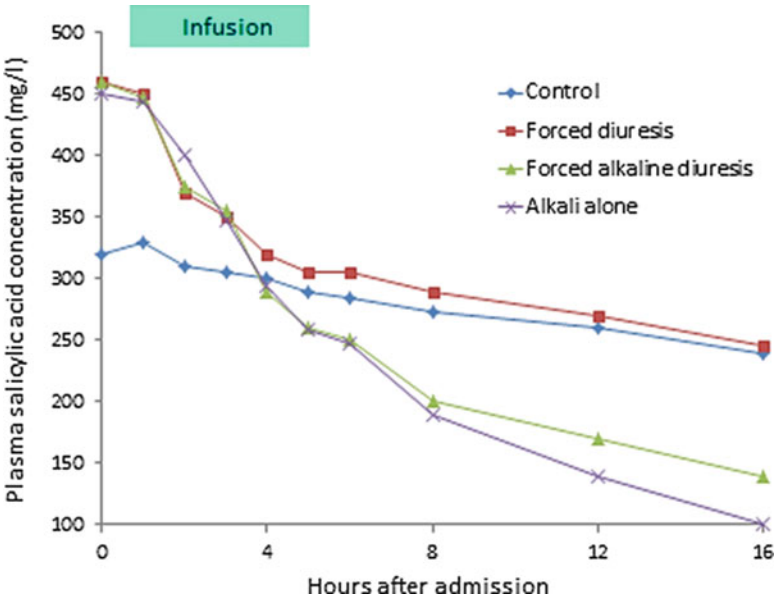

Fig. 27.1 Effects of different treatment regimens (fluid and alkali) on the mean plasma concentrations of salicylic acid in patients with aspirin overdose. Alkalinising the urine promotes ionisation of salicylic acid, reducing salicylate reabsorption and hastening its elimination from the body (Permission from BMJ Publishing Ltd; Br Med J (Clin Res Ed) 1982;285(6352):1383–6)

Clinical Correlation – Caution with Diuresis

In some settings, diuretics are administered to increase the rate of toxicant excretion. Where forced alkaline diuresis is indicated, it is important to first correct plasma volume depletion, electrolyte and metabolic abnormalities, as well as to ensure the renal function is normal before commencing the procedure. Sodium bicarbonate alone is often effective without forced diuresis (Fig. 27.1). Theoretically, urine acidification can promote the excretion of basic drugs, but this procedure is not recommended because it can cause metabolic acidosis.

3. **Use of antidote (interfering with the pharmacodynamics or toxic effects of poison)**

   (a) Neutralization of the circulating toxicant/toxin – this can be achieved with the use of antibody e.g. DigiFab (for digoxin) and antivenom (for venom), or chelating agents such as desferrioxamine (for iron). The rationale is that the therapeutic agent binds (chemically or immunologically) to the toxic agent, rendering it inactive while enhancing its elimination (e.g. immunocomplexes will be phagocytozed).

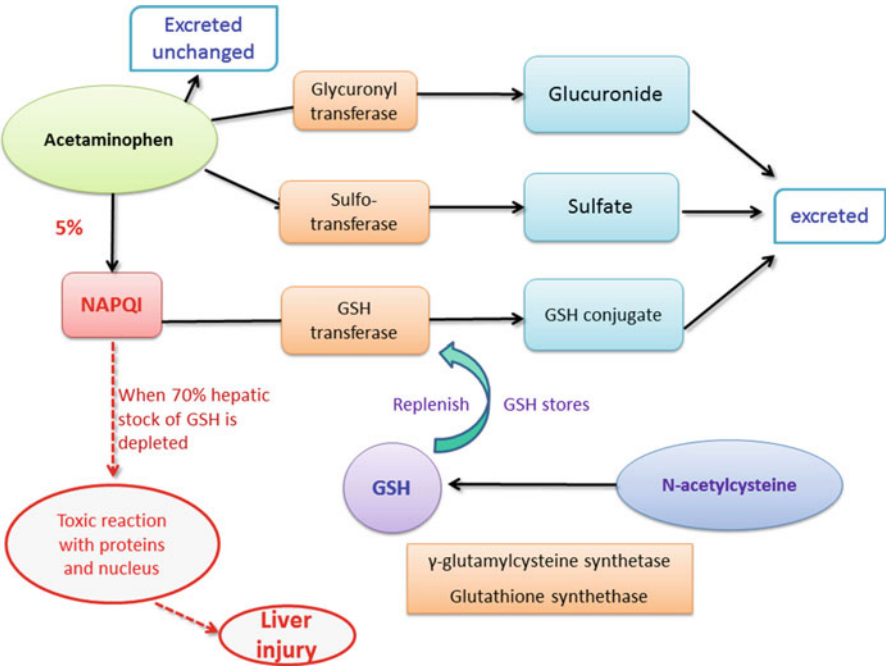

Fig. 27.2 In a healthy adult, almost 95 % of acetaminophen is conjugated with glucuronide and sulfate (Phase II reaction), followed by excretion in the urine. The small amount of hepatoxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), is usually conjugated to glutathione (GSH) for excretion. In acetaminophen overdose, the glutathione stock is depleted, preventing conjugation and resulting in the accumulation of NAPQI that leads to cell necrosis and liver failure. The antidote, N-acetylcysteine, when administered, serves to replenish the GSH for the detoxification of NAPQI

(b) Antagonizing the toxic effects – typically this can be achieved with the use of an antagonist, such as atropine (for cholinergic poisoning), and cholinesterase inhibitor (for non-depolarizing neuromuscular blocker overdose). In organophosphate poisoning that inhibits cholinesterase, pralidoxime is an antidote that reactivates the phosphorylated cholinesterase. Other examples include flumazenil and naloxone that competitively antagonize the actions of benzodiazepines and opioids, respectively (see Chap. 7).

(c) Reducing the generation of toxic metabolite: This is useful for drugs which have toxic metabolites for example, acetaminophen (paracetamol). N-acetylcysteine is an antidote that restores hepatic glutathione, which detoxifies the toxic metabolite, *N*-acetyl-p-benzoquinone imine (NAPQI) (Fig. 27.2).

Clinical Correlation – Beware of Resurgence of the Toxic Effects

The use of antidote to bind circulating antigens (e.g. digoxin, venom toxins) requires careful assessment for rebound phenomenon, especially for drugs and toxins that distribute widely into the tissues (recall: digoxin V_d = 500 L). Immunocomplexation enhances the clearance of the drug / toxin from the vascular compartment, resulting in a sudden shift of the intercompartmental equilibrium and a subsequent resurgence of antigens from the peripheral compartments (tissue-deposited drugs) into the vascular compartment. In the case where a substantial amount of the antidote has been cleared, this can be accompanied with the reappearance of clinical signs, needing prompt management and additional doses of the antidote. This is seen in some snake envenomation where there is a pharmacokinetic-pharmacodynamic mismatch between the venom and antivenom, indicating that the clinical effectiveness of the antivenom needs to be further optimized (Fig. 27.3).

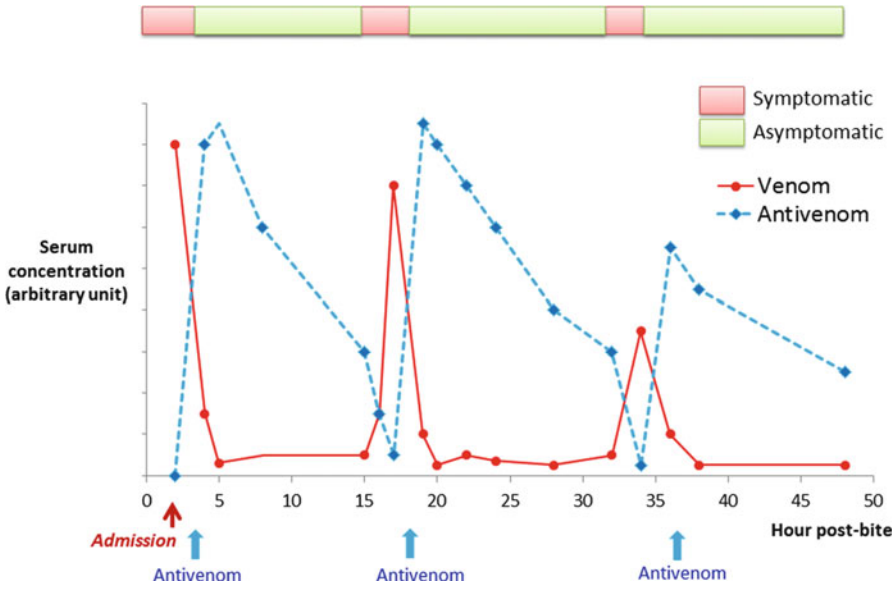

Fig. 27.3 Conceptual representation of venom (*unbroken line*) and antivenom (*broken line*) levels in a patient following snake envenomation. Note the toxic effect subsides (patient becomes asymptomatic, indicated by *green bar*) as the venom level is depleted by antivenom. Rebound phenomenon occurs when the venom level resurges as the antivenom level decreases. This is often accompanied with recurrence of clinical syndrome (e.g. recurrent coagulopathy, recurrent paralysis), necessitating further doses of antivenom to ensure sustained and complete neutralization

Key Concepts

- Drug manipulation can alter the pharmacokinetics (reducing absorption or enhancing elimination) and pharmacodynamics (preventing or ameliorating toxic effect) of toxic substances.
- Choosing the appropriate method of treating poisoning requires good understanding of how different toxic substances are introduced and act on the body. The dose and duration of exposure prior to receiving medical care will determine the appropriate treatment pathway.

Summary

The primary goal in the management of poisoning is to prevent or reduce further injury. In general, supportive care plays a major role in all types of poisoning. Pharmacological approaches, however, are useful to reduce the absorption and to enhance the elimination of the toxic substance. The use of appropriate antidote may prove to be a useful mode of therapy to neutralize the toxic effects of some compounds. Timely administration of appropriate treatment modalities for the acutely poisoned ensures a favorable outcome.

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