

16. ANTIDOTAL THERAPY

The toxicants cause two types of adverse effects: (i) irreversible effects and (iii) reversible effects. The irreversible effects are severe effects induced by the toxicants, such as death of cells or the organisms. On the other hand, the reversible effects include mild to severe effects, but short of death of the cells, tissues or whole animal. The normal cellular or organismic function in case of reversible effects can be achieved in two conditions: (i) on withdrawal of toxicants, and (ii) on treatment of organisms with certain chemicals. *The substances employed to prevent the adverse effects of toxicants are termed as antidotes. The procedures, which are specifically directed toward limiting the intensity of the effect or reversing the effects, are termed as antidotal procedures or antidotal therapy.* The antidotal therapy becomes a necessity when human-beings are involved in the harmful effects of poisons. Hence, most of the development in antidotal therapy is directed toward the protection of human beings from the toxic action of xenobiotics.

(A) *Antidote types* : The antidotes may either be *highly specific*, i.e., a particular antidote can be used only against a particular toxicant, or *universal* or *broad-spectrum antidote*, which may be applied in case of poisoning by unknown toxicants. The universal antidote can be prepared by mixing two parts of activated charcoal, one part magnesium oxide and one part tannic acid. It is useful in case of poisoning by acids, alkaloids, heavy-metals and glucosides.

The antidote may be *simple antidote* that consists of two parts of burnt toast and one part of strong tea. Another simple antidote is carbonate, but it is not suitable in case of acid poisons because of damage to already injured tissues of stomach due to vigorous generation of carbon dioxide.

A *multiple antidote* may also be prepared by dissolving a mixture of animal charcoal (1 part) and magnesium oxide (2 parts) in a mixture of saturated solution of iron sulphate (2 parts) and water (8 parts).

This antidote is effective against arsenic, zinc, mercury, opium, digitales and strychnine poisoning.

Certain *neutralizers*, which convert toxicants into nontoxic substances, can also be used as antidotes. For instance, in case of cyanide poisoning administration of sodium thiosulphate neutralizes cyanide action by forming relatively nontoxic compound, sodium thiocyanate. Tannin is one of the most valuable antidotes acting as *precipitating agent*. It is given in the form of very strong hot tea. Finely powdered activated charcoal adsorbs poison molecules and thus works as *mechanical antidote*.

Various *chelating agents*, viz. desferrioxamine mesylate (for iron poisoning), dimercaprol (for arsenic poisoning) and calcium disodium edetate (for lead and zinc poisoning) with multiple free valencies form stable complex with metallic poisons and facilitate their excretion from the body, thus prevent toxic action of these poisons. These antidotes may either work as *competitive antidotes* when they compete with poisons for the receptor sites or as *noncompetitive antidotes* when they induce certain physiological changes, which may increase the resistance of the organism against the toxic action of poisons.

(B) Antidotal procedures : The antidotal therapy is chiefly based on following three principles :

- (1) Procedures which decrease absorption or translocation of toxicants,
- (2) Procedures which enhance termination of action of toxicants, and
- (3) Procedures, which elevate the threshold of toxicity.

1. Procedures decreasing absorption or translocation of toxicants

The antidotal procedures, which decrease absorption or translocation of potentially adequate amount of ingested poisons, involve two basic approaches :

- (i) Physical removal of poisons, and
- (ii) Use of certain chemicals that may react with, firmly bind with and absorb the toxicants

(i) *Physical removal of poisons* : The poisons can be physically removed from the gastrointestinal tract by following three methods :

- (a) By the use of emetics,

(b) By the gastric lavage, and

(c) By the use of catharitics.

(a) *By the use of emetics* : Emetics produce copious vomiting and help in the removal of bulk of the poison. It is thus an important and life-saving procedure, when the poison is still in the stomach of patient. Therefore, the interval of time between ingestion of poison and induction of emesis should be reasonable in order to ensure that poison is still in the stomach. The poisons once passed into upper intestine would be beyond immediate removal by this procedure. But, these measures should not be attempted if the poisoned patient is unconscious or rapidly losing consciousness or convulsing or shows proconvulsive signs. The induction of emesis should also be avoided in case of poisoning of strong alkali, corrosive acid, kerosene or kerosene like hydrocarbons as also in persons having severe heart disease or pregnancy.

The vomiting is more easily induced and more effective when the stomach is filled with liquid. Hence, age-old first aid dictum for poisoning treatment has been *dilute and wash out*. Dilutions with large quantities of lukewarm liquids slow down the absorption of toxicants. If salt water or soap water is given, both objectives are accomplished simultaneously. It has been advised to place the patient face down with head at lower level than the hips. This checks the entry of vomitus in the lungs.

The simplest emetics are dry mustard (or black mustard powder) and mild soap, which are mixed with warm water and are given to poisoned patient after certain interval followed by lukewarm water. Some of the commonly used emetics are as follows:

(i) *Dry mustard* : One tea spoonful of dry mustard is taken in a glass of lukewarm water. One fourth of this amount is given. This is followed by a glass of warm water. The procedure is repeated after every one minute, until the entire glass has been given.

(ii) *Soapy water* : Shake a piece of mild soap in a bottle of warm water to make suds. Give about one fourth of a glassful and follow a glassful of warm water. Continue until few doses have been given.

(iii) *Ipecac* : Ipecac grain or syrup may be given, if available, to induce emesis. The conventional emetic dose is 15 ml for children and 30 ml for adolescent and adults. Vomiting does not take place immediately after the use of ipecac. The mean latency period ranged from 14-25 minutes, with an average of about 15 minutes in those who vomit after

the first dose. Some workers recommend 10-15 ml syrup of ipecac by mouth to children followed by 6 ounces of water or clear fluid but not milk. To all those patients who fail to vomit within 20-30 minutes after the first dose, a second full dose of ipecac is given.

(iv) Emetic made by mixing sodium chloride (table salt) and copper sulphate have been employed as irritant emetic in treating accidental ingestions, but it does not dependably empty the stomach and both may cause systemic poisoning and death.

(v) *Apomorphine* : Apomorphine has been major rival of ipecac syrup (Table 16.1) as a useful emetic. It is superior to ipecac in terms of its much shorter latency, as vomiting occurs within 2-15 minutes with a mean latency of only 4 minutes. The major disadvantage of apomorphine is its inactivity by oral intake. It is, therefore, generally given through parenteral routes. Second disadvantage is drowsiness and other signs of central depression that apomorphine sometime produces. But, these complications could be eliminated by administering smaller doses (10-30mg/kg) by intravenous route.

(b) *By the use of gastric lavage* : In case of failure of vomiting after emetic treatment and sometime even after vomiting, the unabsorbed poison is physically removed from the stomach by gastric lavage. Generally, it is worth while any time within three hours after ingestion of a poison and sometime even after three hours, if large amounts of milk or cream were ingested by the patient. In children, emesis after intake of ipecac syrup has been found more effective than the lavage. But, if the patient is in coma or in case of rapidly acting systemic poisons, the procedure of choice is prompt administration of activated charcoal and its subsequent removal by gastric lavage.

To remove unabsorbed poison a tube is used alternately to empty and to fill the stomach with a fluid, which is satisfactory vehicle of the poison. Several of these cycles are necessary for effective mechanical washing. The tube is selected in accordance with the poison and patient. In adults and old children oral intubation is preferred to nasal route. In most cases, the composition of wash fluid is less important than its volume or the promptness of lavage. Isotonic saline or tap water is normally used as lavage fluid. But, in some cases solution or solvents are known which chemically inactivate or detoxify the unabsorbed poison. The lavage procedure is practical only for the removal of poisons from the stomach and it is not effective if the poison has passed into the upper intestine.

(c) *By the use of catharitics* : The use of catharitics by poisoned patient hastens the passage of toxicants through the gastrointestinal tract. After one hour of the ingestion of the poison and in case for decreased bowel motility, which slows the passage of ingested toxicants through the gastrointestinal tract, certain oil catharitics and saline catharitics (such as, sodium sulphate, magnesium sulphate, citrates, phosphates, etc.) enhance the passage of bowel, thereby the toxicants. Thus, the toxicity of poisons is reduced or lowered. Generally, saline catharitics are more effective than oil catharitics.

(ii) *Use of chemicals to decrease absorption/translocation of toxicants* :

In addition to physical removal of toxicants from the stomach, their virtual removal may be accomplished by the use of substances that effectively react with, firmly bind with or adsorb with those toxicants. If the chemical nature of toxicant is known, specific substances may be used for the purpose. For instance, to neutralize the caustic action of an alkali sufficient dilute acid may be administered orally. Likewise, some chelating agents, such as calcium sodium ethylene diamine tetra acetic acid, may be administered for chelation with metallic poisons. Both these types of substances quite often result in detoxification of poisons.

(a) *Chelating agents* : These agents are used to reduce the absorption and translocation of metal toxicants. Certain metallic compounds induce toxicity by combining with sulphhydryl groups of essential enzymes and thus inactivate those enzymes. The chelating substances form more stable complexes with metallic toxicants, thereby affecting the absorption of these poisons, ultimately reducing their toxicity. Some common chelating agents are outlined below :

(i) *Desferrioxamine mesylate* : It is a siderochrome, which forms complex with iron and thus works as a powerful chelating agent for iron. It has less affinity for other metals. It is given either orally to block the absorption of iron in the intestine or parenterally to inactivate iron in the circulation. Its complex with iron has low molecular weight and is, therefore, easily excreted by the kidney.

(ii) *Dimercaprol* : It is commonly known as British Anti Lewisite (BAL). It is useful in inactivating the compounds of arsenic, mercury, antimony, bismuth, chromium, cobalt, copper, gold, nickel, zinc and thallium. Dimercaprol-metal complexes are relatively nontoxic and are subsequently excreted in the urine. But, they cause unpleasant side-

effects, such as nausea, vomiting, lachrymation, salivation, abdominal pain and burning sensation in the mouth and throat.

(iii) *Sodium-calcium EDTA* : (Calcium salt of disodium ethylene diamine tetra acetic acid).

It is one of the widely used chelating agents, which forms stable and relatively nontoxic complexes with metallic compounds of lead, iron, calcium, *etc.* The complexes are easily excreted by the kidney along with urine. It is usually given in the form of intravenous infusion. It may also be given intramuscularly, especially to children and orally in case of mild poisoning.

(iv) *Penicillamine* : It forms stable complexes with copper, lead, mercury and thus facilitates the excretion of these metals through the kidney. It is usually recommended to be ingested orally and thus has advantage over EDTA.

(b) *Adsorbents* : Activated charcoal and some other adsorbents may be used to decrease absorption and translocation of toxicants. The usefulness of activated charcoal as a nonspecific antidote depends on its large capacity to adsorb and retain a variety of organic and inorganic molecules and ions including many of common poisons. In adsorbed state, the toxicant produces neither local nor systemic injury and it is eventually eliminated with the charcoal in faeces. However, activated charcoal does not adsorb every poison to a useful degree. For instance, it is useless against ethyl- and methyl alcohol, strong mineral acids and alkalies, cyanides and most water soluble substances. In case of highly toxic poisons, the administered activated charcoal should be removed either by emesis or by gastric lavage.

If activated charcoal is not available, several other adsorbents may be used. For instance, a highly adsorptive clay known as *montmorillonite* is more palatable than powdered charcoal and binds with organic basic toxicants. But, it is inferior to charcoal in case of organic acids. If highly adsorptive clay is not available, some food protein, such as fresh milk, undiluted or evaporated milk, gelatin solution, beaten egg whites, flour and water paste, *etc.* may be used as adsorbents. These proteins adsorb and precipitate some poisons, such as alkaloids, heavy-metal ions and they delay gastric emptying into the duodenum. Thus, the passage of poisons into the blood stream can sometime be retarded. As these proteins are hydrolyzed by digestive enzymes in the stomach and duodenum, the protection is only for sometime. Therefore, poisons adsorbed over these proteins should be removed either by emesis or by

gastric lavage/aspiration, as soon as possible.

Emesis is quite often induced by ipecac and milk is believed to delay the process of emesis. Hence, usually ingestion of all adsorbents and demulscents is postponed until ipecac empties the stomach. But, in case of rapidly acting poisons, such as mercuric chloride, which is quickly and tightly bound to intestinal mucosa, the delayed emesis produced by ipecac is futile. Therefore, in case of ingestion of toxic and corrosive heavy metals, they are first entrapped in the lumen with adsorbents, such as activated charcoal, milk or any other protein solution and then taken out either by injecting an emetic, apomorphine or by gastric lavage.

All the above procedures and agents are concerned with the removal of poisons from the stomach either physically or chemically. But, direct removal of unabsorbed amounts of poisons from intestinal tract is impractical. For the removal of poison from intestine, procedures used are directed toward the prevention of absorption and hastening of transport of toxicant through the intestinal tract, so that it is eliminated in the excreta.

In addition to prevention of translocation of poison from the intestinal tract to blood stream, certain antidotal mechanisms affect the translocation of poison from the blood stream to effector sites. For instance, chelating agents used for the treatment of cyanide intoxication combine with cyanide and detoxify it.

Cyanide owes its toxicity to the inhibition of cytochrome oxidase by forming complex with ferric ion of the enzyme. Therefore, cyanide therapy is directed toward promoting the formation of inactive cyanide complexes before it is able to react with cytochrome oxidase enzyme. Current therapy for cyanide intoxication involves injection of sodium thiosulphate directly into the vascular system. Cyanide reacts with thiosulphate yielding relatively nontoxic thiocyanate, which forms coordination complex cyanomethemoglobin with methemoglobin having considerable stability.

2. Procedures for enhancing the termination of action of toxicants

If the reaction between toxicant and effector is reversible, the antidotal procedures may consist of removal of poisons from the effector sites. The procedures employed to enhance the termination of action of poisons can broadly be divided into two groups :

- (i) Physical procedures, and (ii) Chemical procedures.

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(i) **Physical procedures** : The physical procedures enhancing termination of action of poisons are diuresis, dialysis and haemoperfusion.

(a) **Diuresis** : The basic principles involved in diuresis are ion trapping and increasing urine flow. After glomerular filtration in the renal tubules alteration of the pH of urine can ionize and trap the poisons. Once the poison is ionized, then reabsorption from the renal tubules is impaired, ultimately resulting in its more excretion in the urine. For some poisons forced diuresis by the use of fluids and diuretics may enhance the rate of their elimination. Osmotic diuretics, such as urea or mannitol, are generally more effective than water diuretics.

(b) **Dialysis** : The technique of dialysis, either peritoneal or haemodialysis, is based on the passage of poisons through a semipermeable dialysis membrane and their ultimate removal in dialysate against the concentration gradient. Since the dialysis involves movement of poison molecules, it is partly dependent on the molecular weight of the compound. The poisons, which are highly serum protein bound and having large volume of distribution are either not dialyzable or poorly removed by this method. The lipid dialysis is recommended for the removal of lipophilic poisons, but owing to their large volume of distribution, only a small percentage is removed even after 4-6 hours of dialysis.

(c) **Haemoperfusion** : It is one of the newest techniques in which the blood is passed through a column of charcoal or adsorbent resin for the removal of extracorporeal poisons. Some poisons are better removed by this technique because of absorptive capacity of the column. But, other poisons having large volume of distribution are poorly removed much in the manner similar to haemodialysis. For instance, if the poison is highly bound in fat stores only small amount is available in the blood for removal. At present, only a few substances are available which are able to remove poisons either from fat stores or tissues binding sites.

(ii) **Chemical procedures** : The toxicants produce their harmful effects on account of their interaction with suitable receptors at the specific sites or the site of their action. The removal of poisons from the effector sites before their interaction with receptors terminates their action. The removal of toxicants from other binding sites together with their detoxication by antidotes (antagonistic chemicals) inactivates the poisons in the body of animal. It is not always necessary to

enhance the excretion of poisons from the body of the animal to effectively terminate their action at the effector site. But, the administration of antidotal chemicals form relatively nontoxic complexes with the poisons. Dimercaprol and EDTA are most commonly used chelates, which form inactive complexes with heavy-metal compounds while oximes work as chelates for organophosphorus pesticides.

Most commonly encountered heavy metals are mercury, lead and arsenic. These metals owe their toxicity to primary inhibition of sulphhydryl enzyme systems. These enzyme systems are involved in the production of cellular energy. On administration, the chelating agents form complexes with poisons, which are relatively nontoxic and more stable than enzyme-poison complex. The resultant complex encompasses an unionized form of metal toxicants and their excretion in the urine of poisoned patients increases several folds (about 50 folds in case of Lead-EDTA complex). Thus, the chelates not only detoxify the metallic poisons, but they also promote their elimination from the poisoned patient.

Organophosphorus pesticides owe their toxicity to inhibition of neuroenzyme, acetylcholinesterase and thus disrupt the normal process of synaptic transmission. The enzyme has two active sites :

- (i) anionic site, and (ii) esteratic site.

Inhibition of enzyme by organophosphorus poisons involve their binding with the esteratic site. Administration of oximes to organophosphorus poisoned patient causes binding of these oximes to unoccupied anionic site of the enzyme, leading to the binding of oximes with organophosphorus poisons, ultimately resulting in the liberation of active enzyme. The oxime, therefore, works as antidotal substance, which displaces organophosphorus poisons and thus return acetylcholinesterase-depending physiological mechanism to the normal.

3. Procedures for elevating threshold of toxicity

The antidotes increase threshold of toxicity without affecting the concentration of poisons at the effector sites by following two mechanisms :

- (i) They directly antagonize the system affected by the poisons and enhance a physiologically opposing system, and
- (ii) They block the response produced by the poisons on some physiological mechanism.

Both these mechanisms can be better understood by the following account. The poisons induce toxicity on account of their interaction

with receptors at the specific sites. Thus, a poison induces toxicity by affecting a particular physiological mechanism of organisms. If by the application of some other chemical that physiological mechanism is reversed or antagonized, the poison would not affect the organisms; consequently the toxicological symptoms may not be visible. For instance, barbiturate intoxication decreases the blood pressure and this can be effectively antagonized by the intravenous administration of norepinephrine. Thus, antidotes stimulate a physiological mechanism that is antagonistic to the system affected by the poison.

In contrast to the above mechanism, there are many poisons whose toxic actions can be specifically blocked by another chemical or antidote acting on the same mechanism. Since the poisons act on account of their interaction with certain receptors, the toxic action of poisons can be prevented if the poison is displaced from the receptor or if the same receptor is occupied by an antidotal substance. For example, morphine reacts with the receptor (respiratory centre in the brain) and the product of the reaction causes respiratory depression. An antidote, n-allylnormorphine, also reacts with the same receptor, but cause less respiratory depression. Hence, the application of n-allylnormorphine displaces morphine from the receptor, and the toxic effects are not produced. Another example of use of antidotal chemicals to elevate the threshold of toxicity is the use of atropine as an antidote against muscarine. Alkaloid muscarine, responsible for mushroom poisoning, is believed to react with the same receptor through which acetylcholine induces its effect. The interaction of muscarine with receptor initiates physiological responses similar to those produced by acetylcholine. The effects of muscarine can be prevented by the application of atropine, which also combines with the same receptor. Atropine either displaces muscarine from the site of receptor or it prevents the formation of muscarine-receptor complex. But, it does not directly react with, inactivate or detoxify muscarine molecules.

It may finally be concluded that application of physiologically active antidote requires sufficient background of physiology and pharmacology, so that the objectives of therapy are achieved without induction of added chemical injury. The use of antidotal chemicals are, therefore, restricted to those cases where irreparable damage or death are imminent, and where normal detoxication and excretion mechanisms are not able to cope with the excessive quantities of harmful effects.

Table 16.1. Some common agents useful for antidotal therapy

Drug type	High priority	Lower priority
(a) Adsorbents	Powdered activated Charcoal	1. Cholestyramine
(b) Neutralizers	1. Acetic acid (5%) or vinegar 2. Milk of magnesia	1. Dilute hydrochloric acid (0.5 %) 2. Dilute ammonia water (1%) 3. Sodium bicarbonate
(c) Emetics	1. Ipecac syrup 2. Apomorphine	1. Dry mustard powder
(d) Gastric lavage fluids	1. Water 2. Sodium bicarbonate (3 to 5% soln.)	1. Sodium thiosulphate (1% soln.) 2. Lime water (saturated) 3. Potassium ferrocyanide (0.1% soln.) 4. Potassium permanganate (1:5000) (Prepared with distilled water and filtered) 5. Sodium or Potassium iodide (1% soln.) 6. Calcium lactate (1-3% soln.)
(e) Demulscents	1. Canned condensed milk 2. Milk of magnesia 3. Aluminium hydroxide gel (with or without magnesium trisilicate)	1. Mineral oil 2. Vegetable or cotton seed oil 3. Egg whites (beaten) 4. Powdered milk 5. Starch 6. Bismuth subcarbonate powder
(f) Catharitics	1. Magnesium Sulphate 2. Sodium sulphate	1. Sorbitol (70%) 2. Citrate of magnesia soln. 3. Castor oil
(g) Special antidotes with systemic actions	1. Dimercaprol (BAL) 2. Amyl nitrate 3. Calcium disodium edetate 4. Penicillamine 5. Sodium nitrite 6. Sodium thiosulphate 7. Atropine sulphate 8. Deferrioxamine 9. Naloxone hydrochloride 10. Pyridoxine hydrochloride 11. Physostigmine salicylate	1. Pilocarpine hydrochloride 2. Glyceryl monoacetate 3. Levallorphan tartrate 4. Neostigmine methyl sulphate 5. Leucovorin calcium injection