

## **Review Article**

### **Principles of Toxicotherapy: General & Special Therapy**

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**Abstract:** Appropriate therapies for commonly encountered poisonings, medication overdoses, and other toxicological emergencies are reviewed, with discussion of pharmacists' role in ensuring their ready availability and proper use. Antidotal therapy are general antidotal therapy (supportive and palliative care that palliative treatments may be used to alleviate the side effects of curative treatments, such as relieving the nausea associated with chemotherapy and enhance quality of life; is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy) And special antidotal therapy is the use of any chemical or physiologic procedure used to prevent, minimize, or terminate the adverse effects associated with chemical toxicity or aberrant pathophysiologic processes. These antidotal procedures may alter the toxicity associated with an exogenous chemical (naloxone antagonism of opioid narcotics) or with endogenous substances (epinephrine reversal of histamine-induced anaphylaxis). The goal of this review is to provide essential information to guide the appropriate use of antidotes. Pharmacists can play a key role in reducing poisoning and overdose injuries and deaths by assisting in the early recognition of toxic exposures and guiding emergency personnel on the proper storage, selection, and use of antidotal therapies.

**Keywords:** Antidotal therapy, Palliative care, Toxicotherapy.

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#### **GENERAL (ANTIDOTAL THERAPY)**

##### **Supportive and palliative care**

A World Health Organization (WHO) statement describes palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." More generally, however, the term "palliative care" may refer to any care that alleviates symptoms, whether or not there is hope of a cure by other means; thus, palliative treatments may be used to alleviate the side effects of curative treatments, such as relieving the nausea associated with chemotherapy.

The term "palliative care" is increasingly used with regard to diseases other than cancer such as chronic, progressive pulmonary disorders, renal disease, chronic heart failure, HIV/AIDS, and progressive neurological conditions. In addition, the rapidly growing field of pediatric palliative care has clearly shown the need for services geared specifically for children with serious illness [1].

#### **PALLIATIVE CARE**

**Monitoring:** provides relief from pain, shortness of breath, nausea, and other distressing symptoms; affirms life and regards dying as a normal process; intends neither to hasten nor to postpone death; integrates the psychological and spiritual aspects of patient care;

**Nursing:** offers a support system to help patients live as actively as possible; offers a support system to help the family cope; uses a team approach to address the needs of patients and their families;

**Consulting:** will enhance quality of life; is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy[2].

#### **SPECIAL (ANTIDOTAL THERAPY)**

##### **Availability requirements**

The antidotes listed are considered useful in the treatment of acute human poisoning. Recently, there has been a move away from the older International Programme on Chemical Safety (IPCS) guidelines. Each antidote has its own availability requirement listed

and any slight deviation from the A, B and C classification is noted in each individual entry.

A required to be immediately available (within the Emergency Department). B required to be available within 1 hour (within the hospital) and C these drugs are rarely used and can be held supra-regionally. It would be advisable to know in advance where you can obtain a supply [3].

#### Availability basic mechanisms in antidotal therapy

The ability of any chemical to induce biologic harm is dependent upon two fundamental variables: 1) the amount of chemical to which the biologic entity is exposed (dosage), and 2) the length of time of that exposure. These factors of dosage and time are in turn dependent upon: 1) the total amount of the chemical, 2) its route of administration, 3) its rate of absorption, 4) its ability to traverse membranes, 5) the type and location of its receptor sites, and 6) its rate and degree

of detoxification and/or elimination. These same variables are operant in drug efficacy and drug toxicity.

Antidotal therapy is the use of any chemical or physiologic procedure used to prevent, minimize, or terminate the adverse effects associated with chemical toxicity or aberrant pathophysiologic processes. These antidotal procedures may alter the toxicity associated with an exogenous chemical (naloxone antagonism of opioid narcotics) or with endogenous substances (epinephrine reversal of histamine-induced anaphylaxis).

Three basic mechanisms are available in antidotal therapy to alter toxic drug dosage or time of exposure and thereby the magnitude of the undesired drug-receptor (chemical-biologic) interaction: 1) limiting drug-receptor interaction by altering drug absorption or distribution, 2) protecting the organism by elevating its threshold for toxicity, and 3) hastening the biotransformation and/or elimination of the chemical.

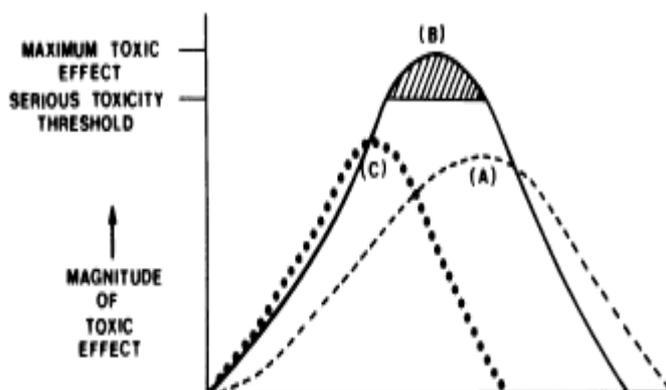


Fig-1: A graphic depiction of the three principles of antidotal therapy.

Curve A illustrates that the ascending portion of the time-effect curve may be decreased by limiting the absorption or distribution of the chemical. Curve B illustrates that the threshold of toxicity may be raised to protect the organism. Curve C illustrates that the descending portion of the time-effect curve may be increased by hastening the biotransformation and/or elimination of the chemical

#### ANTIDOTAL PROCEDURES TO LIMIT DRUG

##### Absorption or Distribution

Any antidotal procedure that restricts the absorption or later distribution of a chemical to its receptor site will do so by preventing or reducing the ability of that chemical to pass biologic membranes. This is accomplished by: 1) removing the drug from the absorbing surface, or 2) chemically altering the drug to change its physicochemical and therefore its pharmacologic or pharmacokinetic properties.

Emesis or gastric lavage physically remove chemicals from their gastric absorption site. If

performed within a reasonable time after drug ingestion (up to two or three hours), physical stimulation of the vomiting reflex or administration of a chemical emetic (such as syrup of ipecac) can function to remove a variable amount of chemical from the stomach. Syrup of ipecac is a gastric irritant as well as a stimulant of the chemoreceptor trigger zone in the area postrema of the brain. It is probably more effective than gastric lavage[4]. Emesis is contraindicated if the patient is in an altered central nervous system state (coma, stupor, delirium) due to the possibility of aspiration of the vomitus, if the chemical is corrosive, or if the chemical is a petroleum distillate [5]. Gastric lavage consists of repeated washings of the stomach with water or innocuous solvents and the removal of the lavage fluids. Once the chemical has passed into the small intestine it cannot be recalled by any procedure.

The classic use of activated charcoal to adsorb the chemical and alter its physicochemical properties as well as prevent its passage across the gastric mucosa is still very effective in specific situations. The usual dose

is two tablespoons in a glass of water (50 mg in 400 ml) [5]. Activated charcoal is more effective than the "universal antidote" (2 parts activated charcoal, 1 part magnesium oxide, 1 part tannic acid) [6].

The neutralization of acids by bases and vice versa is generally unsatisfactory because the antidote may be as corrosive as the poison. Generally dilution by water or milk is best in such a situation [5]. In blood the highly acidic heparin can be neutralized by the strongly basic protamine sulfate as an example of chemical combination antidotal antagonism.

In specific situations, a chemical antidote may interact with the toxic agent to prevent its passage across membranes to its receptor or to produce a less toxic metabolite. Calcium, in the form of milk products or calcium lactate, is an antidote to oral fluoride intoxication as the resulting product (calcium fluoride) is insoluble in water and unable to traverse membranes. Likewise sodium chloride complexes with silver nitrate to form insoluble silver chloride. Heavy metals are rendered inert by chelation with ethylene diaminetetraacetic acid (EDTA).

Decreased formation of a toxic metabolite forms the basis for the use of ethanol as an antidote to methanol poisoning. Methanol is converted by alcohol dehydrogenase (ADH) to a toxic metabolite responsible for optic nerve damage. Because ethanol has a tenfold greater affinity for ADH than methanol, ethanol will occupy active enzyme sites formerly available to methanol and thereby decrease toxic methanol metabolite production. Cyanide intoxication is treated by sodium thiocyanate which results in the less toxic thiocyanate ion as well as by nitrate administration which promotes the formation of the less toxic cyanomethemoglobin.

#### **ANTIDOTAL PROCEDURES TO HASTEN Biotransformation or Excretion**

Any procedure designed to shorten the elimination half life of a chemical will decrease its concentration at receptor sites and its duration in the organism. These half-life alterations are possible by two mechanisms: 1) an increase in biotransformation (detoxification) processes, and 2) an increase in urinary excretion rates.

The enhancement of phase I liver biotransformation reactions (oxidation, reduction, hydrolysis) is theoretically possible but impractical as days may be required for this to occur. The augmentation of phase II conjugation (synthesis) reactions is useful in the management of acetaminophen intoxication where oral antidotal acetylcysteine conjugates and detoxifies the liver-toxic imidoquinolone metabolite of acetaminophen. Ethanol antidotal therapy for methanol poisoning is an exercise in the formation of a less toxic metabolite.

There is no known method to enhance the active transport of chemicals into the urine [5]. It is not feasible to increase the urinary glomerular filtration rate [5]. Osmotic diuretics (mannitol) can increase fluid flow through the kidneys thereby decreasing the rate of solute reabsorption. Bromide intoxication is treated by chloride, which increases the urinary excretion rate of the bromide ion. Dimercaprol (BAL, British Antilewisite) and EDTA form complexes with heavy metals that are more water-soluble and therefore more readily excreted.

An alteration in the urinary pH will change the ratio of ionized to unionized concentrations of some chemicals. Because the unionized portion is more readily reabsorbed in the renal tubules (the ionized portion is more readily excreted), an increase in urinary pH (alkalinization) will increase the excretion of acids (phenobarbital, aspirin) and a decrease in urinary pH (acidification) will enhance the excretion of bases (quinine) [5,7,8].

A knowledge of the basic principles of antidotal therapy, specific antidotal procedures, and support of vital functions is essential for all who administer drugs. So too is the realization that antidotal therapy is not without hazard itself. Naloxone not only antagonizes the respiratory depressant actions of the opioid narcotics but their analgesic action as well. In patients with surgical pain and anesthesia from opioids, the use of naloxone may result in an immediately awake patient without any analgesia who subsequently manifests severe sympathetic nervous system stimulation, cardiac arrhythmias, hypertension, cardiac arrest, and possible mortality [9]. The administration of large amounts of free-flowing oxygen to a patient whose respiration is responsive only to carbon dioxide may result in oxygen apnea. The inappropriate administration of epinephrine to treat a reaction of nonallergic etiology (proper diagnosis is also vital to antidotal therapy) in a patient whose myocardium was sensitized for arrhythmias by chloral hydrate resulted in a life-threatening arrhythmia and possibly necessary mortality [10,11].

As with all drug therapeutics, the outcome of treating drug toxicity is solely dependent upon the knowledge and skill of those using the antidotes.

#### **Antidotal procedures to elevate the threshold of susceptibility**

The organism can be protected from the toxic effects of a chemical without altering its concentration in that organism by: 1) displacing the chemical from its receptor site or preventing its access to the receptor, 2) enhancing the activity of an antagonistic physiologic system or, most commonly, 3) supporting vital system functions (cardiovascular and respiratory) until the toxic

chemical has been eliminated from the organism by natural metabolism and/ or elimination processes.

Specific pharmacologic receptor antagonists are uncommon but highly useful when available. Naloxone is a complete antagonist of the opioid narcotic receptor. Likewise flumazenil (Anexate) is a virtually complete antagonist of the benzodiazepine receptor and will gain importance in the diagnosis and management of benzodiazepine intoxication[12,13]. Atropine antagonizes the muscarinic actions of the organophosphate insecticides and war gases while pyridine-2-aldoxime methiodide (pralidoxime) removes the organophosphates from acetylcholinesterase allowing for resumption of enzyme function.

The classic example of physiologic (functional) antagonism is the use of beta-adrenergic stimulants (epinephrine, metaproterenol) as antidotes to the bronchoconstrictive actions of histamine in anaphylaxis. The beta-adrenergic agent does nothing to alter the tissue levels or receptor interaction of histamine but rather functions to induce a directly opposite physiologic response (bronchodilation) by activating the entirely separate beta-adrenergic receptor.

As there are no specific antidotes for the vast majority of chemicals (less than 2%)[7], most antidotal therapy involves limiting the absorption of the chemical or the maintenance of the support of vital respiratory and cardiovascular systems until the normal detoxification and/or elimination processes reduce the tissue levels of the chemical to below toxic threshold activity[8]. Except for specific antidotal procedures, the most basic principle of antidotal therapy is: "treat the patient, not the poison"[5]. The maintenance of respiration and circulation take precedence unless concomitant removal of the chemical from the body is possible or specific antidotal therapy is available.

## CONCLUSION

Pharmacists can play a key role in reducing poisoning and overdose injuries and deaths by assisting in the early recognition of toxic exposures and guiding emergency personnel on the proper storage, selection, and use of antidotal therapies.

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