Department of Veterinary Pathology

ANTIDOTES IN POISONING

Unit II VPP 609

DR. SANJIV KUMAR
ASSTT. PROFESSOR,
DEPTT. OF PATHOLOGY,
BVC, PATNA

Introduction

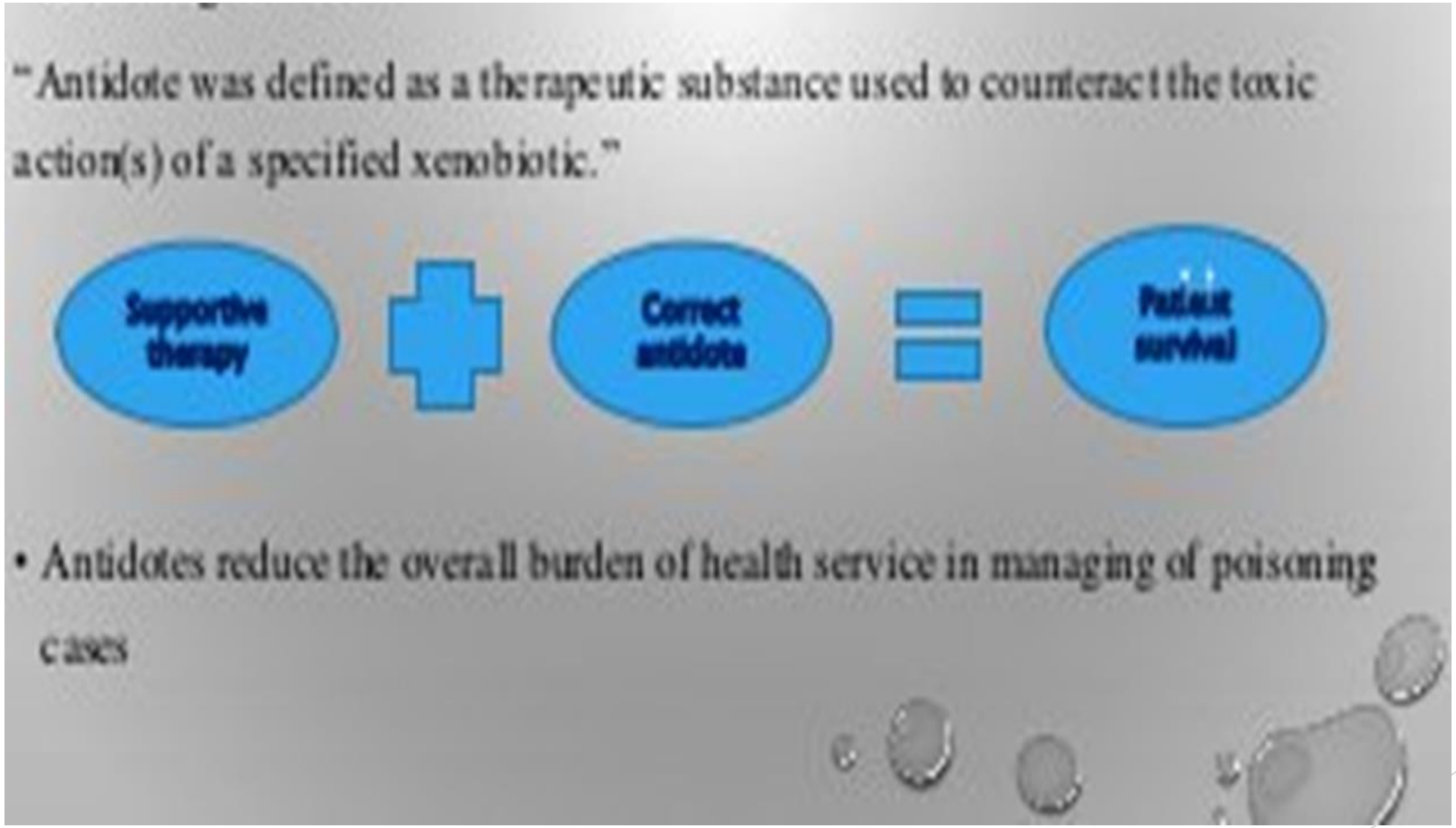
- Antidotes are agents that negate the effect of a poison or toxin.
- Antidotes mediate its effect either by preventing the absorption of the toxin, by binding and neutralizing the poison, antagonizing its end-organ effect, or by inhibition of conversion of the toxin to more toxic metabolites.
- Antidote administration may not only result in the reduction of free or active toxin level, but also in the mitigation of end-organ effects of the toxin by mechanisms that include competitive inhibition, receptor blockade or direct antagonism of the toxin.

Definition

- The International Programme of Chemical Safety broadly defines an antidote as a therapeutic agent that counteracts the toxic actions of a drug/toxin.
- Broadly, antidotes have been looked at as agents that “modify the kinetics of the toxic substance or interfere with its effect at receptor sites.”
- This may be as a result of prevention of absorption, binding, and neutralizing the poison directly, antagonizing its end-organ effect, or inhibition of conversion to more toxic metabolites.

- A chemical's safety is defined by its therapeutic index or ratio (TD_{50}/ED_{50}), which is the ratio of the toxic dose (TD) or lethal dose (LD) to the effective dose (ED).
- Based on this, an antidote has also been defined as an agent that "increases the mean lethal dose of a toxin."

According to WHO



Mechanism of Action

- Antidotes act by four predominant mechanisms;
- (A) Direct action on the toxin involves specific and nonspecific binding and enhanced elimination. Specific binding can be achieved by chelation (e.g., heavy metals), immunotherapy (e.g., digoxin), and bioscavenger therapy (e.g., organophosphorus (OP) compounds).
- Nonspecific binding occurs with the use of activated charcoal and intralipid therapy (e.g., lipophilic local anesthetics (LA) and non-LA drugs). Enhanced elimination of toxin can be facilitated through urinary alkalization (e.g., salicylates, phenobarbital) and hemadsorption with the use of resin or charcoal;

- (B) Action on the toxin binding site can be achieved by competitive inhibition of the enzyme (e.g., ethanol or fomepizole for methanol and ethylene glycol poisoning) or by competitive blockade of the receptor (e.g., naloxone for opioid overdose and flumazenil for benzodiazepine overdose;

- (C) Decreasing toxic metabolites can be done by binding (e.g., *N*-acetyl cysteine (NAC) as for paracetamol overdose) and conversion to less toxic metabolites (e.g., sodium thiosulphate for cyanide poisoning);

- D) Counteracting the effects: drugs such as atropine counteract the muscarinic effects of OP poisoning.
- High-dose insulin euglycemic therapy (HIET) is used for calcium channel blocker (CCB) and β-blocker (BB) overdose.
- Direct antagonism of toxin action is the mechanism for reversing the toxicity of INH (pyridoxine), warfarin (vitamin K), and methotrexate (folinic acid)

Physical Antidote

Agent use to interfere with poison through physical properties, not change their nature

a) Adsorbing: **Adsorption** is the adhesion of atoms, ions, or molecules from a gas, liquid, or dissolved solid to a surface. This process creates a film of the adsorbate on the surface of the adsorbent. The main example is **activated charcoal**

b) Coating: A mixture of egg & milk make a coat over the mucosa.

c) Dissolving: 10% alcohol or glycine for carbolic acid

Universal Anti – dote Activated Charcoal

- Produced by heating pulverized carbonaceous substances sawdust, peat, or coconut shells
- Activation: hot air to erode the internal surfaces of the product and thereby increase its adsorptive surface area.
- Adsorption results from weak intermolecular (van der Waals) forces
- AC can prevent systemic absorption of drugs when given within 1-2 h of ingestion
- the optimal dose is probably a 40:1 ratio (by weight) of charcoal to drug
- Contraindicated for iron, lithium, potassium, and ethanol overdose

Chemical Antidote

- Interact specifically with a toxicant, or neutralize the toxicant.

E.G. Metal chelators combine with metals to form complexes that can then be eliminated by the kidneys

Mainly act by two mechanisms:

- Complex formation:

Antidote make complex with the toxicant making it unavailable to cross the membrane or to interact with receptors

- DMSA (dimercaprol and dimercaptosuccinic acid are sulfohydral compounds that bind metal such as arsenic acid ,lead.

- Sp. Binding agents like EDTA, defroxamine and d-pencillamine act by chelation of metal forming more water soluble complex
- Antivenins and antibodies against digitoxin are immunologicaly genrated agents that bind specifically to the toxin or venom

➢ Metabolic conversion:

Detoxification to less toxic product

- Nitrite interact with hemoglobin and cyanide to form cyanomethamoglobin , which is less toxic than cyanide and interfere with the cyanide access to cytochrome oxidase system.

WHEN BE ADMINISTERED?

- The “benefit from antidotes is generally time-dependent and uncertain.”
- It is difficult to give a prescribed approach to guide the decision to administer an antidote in a toxicological emergency as this depends on the lag time to presentation, toxicokinetics properties, and the mechanism of action of the antidote.

- Antidotes that decrease the toxin level by reducing absorption or by adsorption (binding agents) at the receptor/enzyme level are generally beneficial if administered early.
- On the other hand, antidotes that modify the toxic metabolites or modulate the effects (either symptomatic or direct antagonism of the effect of the toxin) could be given at variable times.

HOW LONG THE ANTIDOTE BE ADMINISTERED?

- The duration of antidotal therapy depends on the type of toxin consumed, the estimated dose that the individual has been exposed to, route of exposure, clinical features of toxicity, half-life, and pharmacokinetics as well as the risk vs benefit for the use of the antidote.
- In case the antidote has a short half-life, an infusion may need to be started particularly if symptoms of toxicity resurface.

CONCLUSION

- Successful outcomes in a toxicological emergency not only require appropriate management of airway, breathing, and circulation but also the knowledge and application of appropriate antidotal therapy.
- The latter may result in reducing the intensity of the poisoning and improving outcomes.

THANK YOU