ISSN: 2521-0815 (Print)
ISSN: 2521-0432 (Online)

Contents List available at RAZI Publishing

Matrix Science Pharma (MSP)

Journal Homepage: http://www.razipublishing.com/journals/matrix-science-pharma-msp/

PRACTICAL ASPECTS OF TREATMENT OF ORGANOPHOSPHATE AND CARBAMATE INSECTICIDE POISONING IN ANIMALS

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ARTICLE DETAILS

Article history:

Received 22 January 2017
Accepted 03 February 2017
Available online 05 February 2017

Keywords:

ABSTRACT

Organophosphate insecticides are one of the most commonly used insecticides in crop production in Pakistan. Some of the common organophosphates and examples of their brands used as crop pesticides in Pakistan include dimethoate (SystoateTM Aventis, Germany), monocrotophos (NuvacronTM, Switzerland), acephate (OrtheneTM, Valent, USA), malathion (FyfanonTM, Jaffer Group, Pakistan), profenofos (CuracronTM, Syngenta Pakistan Ltd.), triazophos (DiplomatTM, Four Brothers Group, Pakistan), chlorpyrifos (LorsbanTM, Dow Agro Sciences, Pakistan). In veterinary practice, they are commonly used either as anthelmintics (e.g. dichlorvos, trichlorfon (NeguvanTM, Bayer, Germany; SantrifonTM, Sanna Labs., Faisalabad; TagafonTM, Star Labs., Lahore), haloxon, crufomate, coumaphos and naphthalophos) or as ectoparasiticides (e.g. trichlorfon, chlorfenvinphos, chlorpyriphos, coumaphos, diazinon, dichlorvos, fenthion, malathion, phosmet, ronnel, famphur and tetrachlorvinphos). Carbamates are also commonly used insecticides. Only two carbamatesviz. carbaryl and propoxur are used as ectoparasiticides in animal practice. No carbamate preparation is available for veterinary use in Pakistan.

1. Introduction

Organophosphate insecticides are one of the most commonly used insecticides in crop production in Pakistan. Some of the common organophosphates and examples of their brands used as crop pesticides in Pakistan include dimethoate (SystoateTM Aventis, Germany), monocrotophos (NuvacronTM, Switzerland), acephate (OrtheneTM, Valent, USA), malathion (FyfanonTM, Jaffer Group, Pakistan), profenofos (CuracronTM, Syngenta Pakistan Ltd.), triazophos (DiplomatTM, Four Brothers Group, Pakistan), chlorpyrifos (LorsbanTM, Dow Agro Sciences, Pakistan). In veterinary practice, they are commonly used either as anthelmintics (e.g. dichlorvos, trichlorfon (NeguvanTM, Bayer, Germany; SantrifonTM, Sanna Labs., Faisalabad; TagafonTM, Star Labs., Lahore), haloxon, crufomate, coumaphos and naphthalophos) or as ectoparasiticides (e.g. trichlorfon, chlorfenvinphos, chlorpyriphos, coumaphos, diazinon, dichlorvos, fenthion, malathion, phosmet, ronnel, famphur and tetrachlorvinphos).Carbamates are also commonly used insecticides. Only two carbamatesviz. carbaryl and propoxur are used as ectoparasiticides in animal practice. No carbamate preparation is available for veterinary use in Pakistan.

Organophosphate and carbamate poisoning occurs when fodders sprayed with these insecticides are consumed by animals. Consumption of weeds harvested as animal feed from cotton fields sprayed with organophosphate insecticides is a common mode of exposure to these insecticides. Consumption of cotton seed cake containing residues of insecticides sprayed on cotton crop has been incriminated in deaths of hundreds of cattle and buffaloes at Landhi Cattle Colony, Karachi. Poisoning due to use of veterinary organophosphates is quite rare although their use in debilitated and stressed animals even when used as per the manufacturers' directions may sometimes lead to appearance of signs of toxicity.

Both organophosphates and carbamates produce their effects by inhibiting the acetylcholinesterase enzyme. This enzyme inhibits the action of acetylcholine (a neurotransmitter essential for transmission of impulses between nerves). Therefore, most signs of organophosphate and carbamate poisoning are due to accumulation of acetylcholine.Organophosphates inhibit acetylcholinesterase irreversibly. Carbamates on the otherhand, inhibit this enzyme reversibly.

2. Clinical signs

Severity of clinical signs of organophosphate and carbamate poisoning depends mainly upon the quantity of the insecticide which the animal has been exposed to. Moderate to severe toxicity causes the following signs (McKellar et al., 1998; Radostits et al., 2007; Grecco et al., 2009; Oehme, 2017):

Excessive salivation, depression,miosis (constriction of the pupil of the eye), dyspnea with shallow respirations, colic and diarrhea due to increase in intestinal motility, frequent urination, restlessness, patchy sweating (in horses only),moderate to marked bradycardia, seizures, muscular tremors, incoordination of movement (ataxia), weakness of hind limbs, flaccid paralysis and paresis followed by recumbency and high death rate. Death is due to respiratory failure (anoxia).

3. Diagnosis

Field diagnosis is based on history of exposure to organophosphate or carbamate insecticide and clinical signs. An effort should be made to search the container of the insecticide which may help to know the nature of the insecticide. Determination of cholinesterase activity in blood and brain may be helpful in lab. diagnosis (Oehme, 2017). Samples of stomach and rumen should be submitted in refrigerated form (not frozen) for lab confirmationof organophosphate/carbamatepoisoning.Postmortem lesions are not nonspecific. However, according to Oehme (2017), the commonly observed postmortem findings include:

a) Accumulation of large quantities of fluids in the lungs, mouth and digestive tract
b) Bands of hyperemia (1-7 cm) in the mucosa of small intestine may be present in some animals due to excessive peristalsis
c) Empty urinary bladder due to excessive urination
d)Presence of liquid feces in the colon

Organophosphate and carbamate poisoning may be confused with other types of poisonings, in particular pyrethroids (e.g. cypermethrin, deltamethrin, lambda cyhalothrin, bifenthrin) poisoning. Some of the signs (e.g. excessive salivation, tremors and seizures) occur both in pyrethroids poisoningand in poisoning due to organophosphate and carbamate. Due to similar clinical signs, veterinarians may make the mistake of using atropine to treat animals suffering from pyrethroid poisoning. There is no antidote for pyrethroid insecticides.

Atropine is not only ineffective for pyrethroid poisoning but may also increase their toxicity because it can increase CNS stimulatory effect and tachycardia. Therefore, it is important to know whether the animal has been poisoned by organophosphate/carbamate or by some other poison. Due to accumulation of very high levels of acetylcholine in the body, constriction of the pupil of the eye (miosis) is an important sign of organophosphate/ carbamate poisoning. Therefore, the eye of the animal suffering from

suspected insecticide poisoning should be thoroughly examined for this important clinical sign. A practical field method (therapeutic diagnosis) to differentiate between poisoning due to acetylcholinesterase inhibitors (organophosphate and carbamate insecticides) and other poisonings (e.g. pyrethroids) is to treat the suspected animal intravenously with a pre-anesthetic dose of atropine (0.02 mg/kg). If this low dose of atropine produces anticholinergic signs such as tachycardia and mydriasis (i.e. dilatation of pupil of the eye), then the animal is not suffering from organophosphate or carbamate insecticide poisoning. In animals which are suffering from organophosphate or carbamate poisoning, at least 10 times (0.2 mg/kg) higher dose of atropine would be required to produceanticholinergic signs such as tachycardia and mydriasis (DeClementi, 2007; Fikes, 1990).
Treatmentof organophosphate and carbamate poisoning is based on:

a) Immediate removal of contaminated feed and water.

b)Thorough washing of the animal with soap and water is indicated when exposure to organophosphate and carbamate insecticides has occurred through the skin.

c) Administration of atropine (e.g. Inj. AtrosinTM 1mg/ml, P.D.H. Lab. Pvt. Ltd. Pakistan; Inj. AtrostarTM1mg/ml, Star Labs. Lahore; there are several human brands as well). The first injection of atropine should be given at the following dose rates:

Cattle	=	30 mg per 50 kg of body weight
Horses	=	6.5 mg per 50 kg of body weight
Sheep	=	50 mg per 50 kg of body weight

One fourth to one third of the above recommended average initial doses should be given by slow intravenous injection and the remainder intramuscularly or subcutaneously. After the symptoms are under control repeat the maintenance dosesaccording to the response of the animal to atropine injection.The usual dose rate in dogs and cat is 0.2 -2.0 mg/kg every 3-6 hours or as the situation dictates. An adult cow may need 100 ml or more of atropine injection (Oehme, 2017).Proper atropinization is indicated by mydriasis (dilatation of pupils), stoppage of salivation and alertness of the treated animal.Atropine is able to block the effects of anticholinesterase agents at the muscarinic receptor sites.However, there is no effect of atropine on the neuromuscular junction as well as autonomic ganglia where accumulation of acetylcholine leads to weakness and ultimately paralysis of skeletal muscles including those involved in respiration (DeClementi, 2007).

d) Administration of cholinesterase enzyme re-activators(oximes) such asobidoxime (Inj. ToxogoninTM, E Merck, AD Marker) @ 5mg/kg intramuscularly or slow intravenously or pralidoxime mesylate (2-PAM; Inj. ContrathionTM 200mg/10ml, Acti-Med Pharma, Pvt. Ltd.Pakistan or Inj. D-OximeTM200mg/10ml, Atco Lab. Ltd. Pakistan;both brands are expensive for general veterinary use) @ 20-40mg/kg intravenously repeated at 4-6 hours interval. Oximes are recommended for treatment of organophosphate poisoning but not needed for carbamate poisoning (McKellar et al., 1998).They act by causing dissociation of the enzyme-organophosphate bond (Barragry, 1994). Oral administration of activated charcoal is indicated to prevent absorption of insecticide that is still present in the gastrointestinal tract. Owing to large quantities of rumen contents, activated charcoal is less effective in ruminants than in carnivores. Activated charcoal has a microporous structure that provides a large adsorptive surface onto which a variety of compounds/poisonous substances are readily adsorbed. The dose is 1-2kg for adult cattle and is given in the form of a slurry(prepared by adding water @ 1g of activated charcoal to 5ml of water)through the stomach tube. Its administration must be accompanied or followed by oral administration of a cathartic such sodium sulphate @ 1 gm/kg. Magnesium sulphate @ 1 g/kg can also be used but is less effective than sodium sulphate (Oehme, 2017). Cathartics are not recommended for use in animals suffering from severe diarrhea and dehydration (DcClementi, 2007).Activated charcoal adsorbs the toxic substances and makes them unavailable for absorption through the gastrointestinal tractthus facilitating their expulsionfrom the body through the feces. Activated charcoal-sodium sulpahte is a broad spectrum adsorbent indicated in the treatment of insecticides, pesticides, anthelmintics,fungicides, herbicides, rodenticides, plant alkaloids, feed additivespoisonings as well asmycotoxins and bacterial toxins(Barragry, 1994).Ideally, small animals to be treated with activated charcoal should be sedated and a cuffed endotracheal tube passed to prevent.

e)Supportive treatment (Oehme, 2017):

(1) Place the severely affected animal in the lateral position with head lower than the feet to reduce the chances of aspiration pneumonia resulting from regurgitation of stomach contents.

(2) Induction of vomition in those dogs and cats which are still conscious and are at an early stage of poisoning. Hydrogen peroxide (3%) given orally @ 1-2ml/kg (but not more than 50ml) is an effective emetic in dogs and cats (DeClementi, 2007). Alternatively, common salt (1 teaspoonful) can be carefully thrown at the back of the mouth of the poisoned but conscious dog and cat. Xylazine HCl (e.g. Inj. XylazTM, Fatro Pharma) @ 0.44 mg/kg intramuscularly can also be used to inducevomition in cats which occurs within 5 minutes of its administration. It is not a predictable emetic in dogs (DeClementi, 2007).Use of emetics is usually most effective within 2-3 hours of ingestion of an insecticide.

(3) Gastric lavage is recommended in situations where use of emetics is not advisable or in species (e.g. ruminants) which do not vomit. If the poisoned animal is not unconscious, general anesthesia should be given and an endotracheal tube passed before starting gastric lavage.Several stomach washes (using about 250ml of water containing 5-25g of activated charcoal for each wash)should be given in dogs. After several stomach washes, about 200ml of water containing activated charcoal should be placed in the stomach and not aspirated.

(4) Fluid therapy to maintain proper kidney function and systolic blood pressure by intravenous administration of dextrose 5% with normal saline or Ringer's solution.

(5) Maintaining vital body functions, in particular respiration by oxygen therapy/intubation and heart activity by slow intravenous administration of calcium gluconate and digoxin (@ 0.2-0.6 mg/kg).

(6) Constant monitoring of pulse, respiration and pupil size.

(7) Measures to maintain body temperature by covering with a blanket (if the weather is cold) and washing the body with cold water (if there is hyperthermia).

(8) Controlling CNS hyperactivity by intramuscular or intravenous administration of diazepam @ 0.5-1.5 mg/kg.

(9) Organophosphates and carbamates cause an oxidative stress as indicated by increase in reactive oxygen species (ROS), increase in lipid peroxidation products and decrease in ATP (Milatovic et al., 2006). Acetylcysteine + vitamin C is a broad spectrum antioxidant combination which has not as yet been investigated in the treatment of organophosphate or carbamate poisoning. However, in view of a broad spectrum nature of this combination, easy availability as well as its effectiveness in a variety of other poisonings, its use is probably justified in the treatment of organophosphate or carbamate poisoning. For cattle, buffaloes or horses, dissolve 15 sachets of Mucolator® (Acetylcysteine 200mg per sachet; Abbot Lab. Ltd.,Pakistan) in 500ml of distilled or mineral water (e.g. Pure Life®, Nestle). Filter this solution through 4 layers of muslin cloth ('Mulmal ka kuprra' in Urdu). Add this filtered solution to one liter of warm dextrose 5% solution and inject intravenously. In conscious cows, buffaloes or horses, intravenous administration of Mucolator® should be followed by administration of 30 tablets of vitamin C (e.g. Tab. Cecon®, Abbot Lab.) in the form of a drench. Repeat intravenous administration of Mucolator®and oral administration of Tab. Cecon®at 12 hours intervalfor the next 2 to 3 days. Other antioxidants (e.g. vitamin E) can also be used to reduce the oxidative stress (Milatovic et al., 2006).

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Cite this article as: Ghulam Muhammad, Imaad Rashid and Sehrish Firyal. PRACTICAL ASPECTS OF TREATMENT OF ORGANOPHOSPHATE AND CARBAMATE INSECTICIDE POISONING IN ANIMALS / Mat. Sc. Pharm 1(1) (2017) 10-11