

Rational *Drugs*

An Update on Rational Drug Use

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REVIEW TOPIC — POISONING — CHEMICAL, DRUGS & BITES

Interventions for the Treatment of Organophosphorus Pesticide Poisoning

Self-poisoning with Organophosphorus (OP) pesticides is a major problem across the Asia Pacific region. They cause the majority of poisoning deaths in India, except in some northern areas where aluminium phosphide predominates. There is no effective treatment for aluminium phosphide poisoning; in contrast, moderately effective treatments and antidotes exist for OP poisoning which if used well can reduce mortality. However, the evidence for most interventions is weak and more effective therapies are required if the case fatality ratio is ever to be consistently reduced to below 10%.

PATHOPHYSIOLOGY

The effect of OP pesticides is due to the inhibition of acetylcholinesterase (AChE) in synaptic clefts of the neuromuscular junction, autonomic nervous system, and CNS. Acetylcholine is no longer broken down, resulting in sustained stimulation of post-synaptic receptors and the classic picture of OP poisoning described in every textbook. Deaths occur acutely due to respiratory failure or cardiovascular collapse,

This issue has attempted to cover three different areas of poisoning – chemicals, medicines & bites that are encountered by patients, doctors and health workers frequently. The articles are contributed by eminent persons or institutions and the editorial team thankfully acknowledges their efforts.

and later due to peripheral respiratory failure and the complications of aspiration and long term ventilation.

RESUSCITATION

Effective and rapid resuscitation of patients with stabilisation of the airway is essential for a good outcome. Ventilation will be required for a significant number of patients.



ATROPINE

Administration of atropine is fundamental to the management of OP poisoning. Atropine antagonises acetylcholine's effects on muscarinic receptors and treats the early parasympathetic features of OP poisoning, increasing the heart rate and blood pressure and reducing excess fluid and bronchospasm in the lungs.

Stabilisation of the patient requires rapid administration of intravenous atropine to improve cardiac and respiratory function – to 'atropinise' the patient. Although this has been standard practice for many years, the ideal regimen is still not known. A review of textbook recommendations on patient atropinisation found 35 different regimens. Most were not specific, suggesting doses such as 1-5mg, every 5-20 minutes; some

would have required several hours to give 25mg.

The fastest method to atropinise patients is to give a 1-3mg initial bolus of atropine and to see whether it reverses sweating, bradycardia, hypotension, bronchospasm, and bronchorrhoea. If there is no response at five minutes, the dose is doubled and doubled again until there is a clear improvement in the patient's condition – using very large boluses if necessary. This method is preferred since rapid stabilisation of cardiorespiratory function is required and it results in the fastest administration of atropine among the regimens reviewed.

There has been only one published controlled trial of atropine. It found that boluses followed by an infusion were more effective than boluses alone; however, the study may have over estimated the benefits as it used historical control patients. In the absence of better evidence, the World Health Organization (WHO) currently recommends the use of boluses followed by an infusion to keep patients atropinised.

OXYGEN AND IV FLUIDS

Textbooks often state that atropine should not be given until the patient has been given oxygen, because of a risk of inducing ventricular dysrhythmias. However, the evidence for this is weak and atropine can be given routinely to patients before oxygen is available without inducing dysrhythmias. While it is preferable to give oxygen to OP

poisoned patients, the absence of oxygen should not prevent the urgent administration of atropine in small rural hospitals since atropine will improve patient oxygenation by reducing bronchospasm and bronchorrhoea, and increasing the heart rate.

The increased secretions found in OP poisoning produce intravascular volume depletion. Administration of 500-1000ml of normal saline in a severely poisoned patient should be considered.

PRALIDOXIME

The effectiveness of oximes such as pralidoxime is unknown. However, the WHO currently recommends a loading dose of at least 30mg/kg given over 20-30 minutes followed by an infusion of at least 8mg/kg/hr. Too fast administration of the bolus induces vomiting that risks aspiration. A randomised controlled trial (RCT) is now underway in Sri Lanka to test the effectiveness of this regimen.

An RCT carried out at the Christian Medical College, Vellore, reported increased incidence of respiratory failure and death in patients who received 3-4g of pralidoxime/day as an infusion, but no loading dose. This result appears to contrast with clinical

studies carried out in Germany and may be explained in part by the long interval between poisoning and hospital admission in the study (median 12hrs). This long delay would have had two consequences: changes in the inhibited AChE ('ageing') in patients taking dimethyl OPs such that pralidoxime could not have worked, and an opportunity for complications such as aspiration or anoxia to have occurred before admission (patients may have died of these complications which would not have been affected by oximes).

Some OP poisoned patients are unlikely to benefit from oxime therapy – for example those with severe complications from the pre-hospital period, those presenting after 12 hours with dimethyl OP poisoning, and those with very severe poisoning in which high OP blood concentrations simply re-inhibit the AChE that the pralidoxime has just reactivated.

More recent studies also suggest that S-alkyl OPs such as metamorphos and profenofos age very quickly and require oxime therapy to be started within minutes, rather than hours. In the context of the rural Asia, this is not practical and such OPs may be best considered as not responding to pralidoxime. Despite these caveats, it is probably best at the moment to treat all patients with OP poisoning

with pralidoxime until definitive studies, with identification of OPs, are reported.

GASTRIC DECONTAMINATION

Gastric decontamination is unlikely to benefit most patients as OPs are rapidly absorbed. Thus, gastric lavage or activated charcoal

should not even be considered until the patient has been resuscitated and stabilised with administration of atropine, fluid, and oximes. In patients who have not received atropine, the passage of a large orogastric tube risks inducing vagal responses that can result in asystolic cardiac arrest. Lavage in a struggling patient also has a high risk of causing pulmonary aspiration of the pesticide and its solvent. Thus lavage should only ever be performed in a cooperative or intubated patient.

Forced emesis by any means is not recommended since patients may rapidly lose consciousness and their airway control while vomiting, risking aspiration. Preliminary results of a large RCT of activated charcoal performed in Sri Lanka showed no effect of superactivated charcoal in OP poisoning. However, until this study is formally analysed and reported, it seems reasonable to give a single dose of charcoal to all patients presenting with 2 hours.

OTHER DRUGS

Diazepam is used for the treatment of OP induced seizures, and can also be used to reduce agitation. In the absence of good information about the level of brain damage in poisoned patients, it is not yet possible to determine the role of routine use of CNS sedatives such as NMDA blockers or diazepam. Bicarbonate is used in Iran and Brasil for OP poisoning but clinical studies have not shown benefit.

FUTURE TREATMENTS

The current regimen of resuscitation, oxygen, atropine, oximes and diazepam is only partly effective, with case fatality ratio over 10% being common in many hospitals. There are many other possible interventions that need to be taken through clinical development and, if effective, provided at an affordable cost.

References for this information can be found online at <http://ccforum.com/content/8/6/R391>

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Down To Earth

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