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W3. Venkatesh S, Kavitha ML, Zachariah A, Oommen A. Progression of type I to type II paralysis in acute organophosphorus poisoning: is oxidative stress significant? *Arch.Toxicol.* 2006;**80**:354-61.

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W5. Amitai G, Moorad D, Adani R, Doctor BP. Inhibition of acetylcholinesterase and butyrylcholinesterase by chlorpyrifos-oxon. *Biochem.Pharmacol.* 1998;**56**:293-9

W6. Rotenberg JS,.Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics* 2003;**112**:648-58.

Reviewers' comments and authors' responses

Reviewer 1, Professor D N Bateman, Director, NPIS Edinburgh

This manuscript is an up to date review on organophosphorus pesticide poisoning. Its purpose is set out in the introduction. The manuscript has been written from an international perspective, some of the statements in it may not be absolutely relevant to a UK perspective. Thus, in the section "Why do I need to know about acute OP poisoning?" the authors state "Household and agricultural products containing OPs are prevalent and uncontrolled . . ." This statement would not be seen as accurate from a UK perspective, but I appreciate is relevant to the area where Dr Roberts is currently working.

Authors

OP pesticides are easily obtained from pet stores, supermarkets, pharmacies and home and garden stores in many parts of the world. In developed countries these products are becoming increasingly regulated, but still available. We have deleted 'controlled' from this sentence since the degree to which OPs are controlled (eg. government regulations) is somewhat variable.

Reviewer

From a Northern European perspective the problem of OPs is a minor one, but from a worldwide perspective it is particularly important in developing countries where pesticides are widely. It may also be more relevant in southern Europe for the same reason. The authors may wish to look at a UK perspective (see NPIS annual report http://www.hpa.org.uk/chemicals/npis_reports.htm) which illustrates the relatively benign nature of organophosphate exposure in the UK and perhaps this should be included to balance this review for the different audiences who will read it. It is unlikely that any intensive care unit in the UK will have had experience of organophosphate

poisoning. Nevertheless this is not a reason not to publish this article in the BMJ, merely a plea for some balance in the presentation.

Authors

It was stated in the introduction that while the incidence of severe OP poisoning in developed countries is low compared to developing countries, there are disproportionately more cases of low dose exposure requiring assessment and management. To clarify this we have made minor alterations to the text to clarify this difference in severity between countries. However, in general, we think it is unwise to convey that OP poisoning is of a relatively benign nature in case this leads to complacency with the assessment and management of such cases. There were a number of deaths attributed to acute OP poisoning prior to 1989 (Hum Exp Toxicol 1994; 13: 95-101), but limited information since then. There was a recent case report of severe OP poisoning from the UK which required prolonged ICU admission (QJM 2004; 97: 75-80), and the NPIS Reports in 2003 & 2004 state that cases of severe OP poisoning were reported to them (recognising the potential bias of this data in terms of notifications to the NPIS and limited follow-up of clinical outcomes).

Reviewer

The authors may wish also to stress more clearly the differences between exposure and poisoning with regard to risk classification. In the UK, for example, organophosphate poisoning (as opposed to exposure) is really only likely from deliberate ingestion of concentrate or perhaps in a child who may ingest a newly loaded animal treatment collar. This therefore may influence the order in which the authors wish to present their material. Logically, in a Northern European setting the majority of patients will have mild or no clinical toxicity, and I wonder if that should be the first item, rather than leaping into the more serious cases which are of course are so unusual in our clinical environment.

Authors

The manuscript discusses asymptomatic and mild poisoning in the first instance, followed by moderate to severe poisoning, which is consistent with this suggestion.

Reviewer

In clinical practice, patients presenting to emergency departments are often unaware whether they have swallowed a carbamate or an organophosphate insecticide and perhaps the authors should make some comment on this.

Authors

We focus on the importance for clinical assessment and cholinesterase assays, if available. In the manuscript there is a specific section regarding carbamates and how they differ to OPs, including treatment recommendations that if in doubt, it can be treated as an OP poisoning until further information is available. We have also briefly mentioned two important differential diagnoses for OP poisoning.

Specific comments from reviewer

Introduction - the description here does not really match UK or Western Europe. See above. This section probably ought to be re-written to reflect a wider range of experience than just south-east Asia and the Southern United States.

Authors

This has commented on to a degree above. Depending on how Europe is divided, there are many reports of severe acute OP poisoning from Germany and Spain, which is similar to personal experience in Australia and other developed countries.

Reviewer
Control of marketed product is obviously a key factor in whether or not toxicity is likely from accidental overdose. Such controls tend to be applied in Western Europe.
Authors
We have restricted this clinical review to the assessment and management of acute OP poisoning. We agree with Professor Bateman's comments, but do not have space to further discuss regulatory approaches to pesticide (and other) poisoning in this review.
Reviewer
Page 8, line 4 - preferred term is Europe is "clinical toxicologist", "medical toxicologist" is a US term, not generally accepted elsewhere.
Authors
Accepting the fact that medical toxicologist is a US term, there are a large numbers of US readers. This is a politically charged topic in the US and listing both medical and clinical toxicologist is a small concession to this issue.
Reviewer
Page 14, box 2 - first section should be home and garden, perhaps rather than just home, and this would then be divided into two sections. The term veterinary preparations is perhaps slightly misleading. Many pet collars are actually available from pet shops and therefore not strictly veterinary preparations available on prescription.
Authors
We have altered the title to "Home and Garden", but did not think it was necessary to further sub-divide the section. Similarly, "veterinary preparations" has been changed to 'Pet preparations."
Reviewer
Industry/occupational - what about use of insecticides in the context of pest control within buildings?
Authors
We have also included "general pest control, including fumigation."
Reviewer
Box 4 - oximes - although the authors state two types of oximes are available there are different salts of pralidoxime and it is suggested that some may be different to others. Do the authors wish to comment further?
Authors
We have modified Box 4 to reflect the availability of other oximes. There is inadequate data regarding the differences between individual salts of pralidoxime for it to be necessary to discuss the issue in this clinical review.
Reviewer
Actually other oximes are also available for CBRN incidents too -?? comment too.
Authors
The use of HI-6 is generally limited to auto-injectors for the treatment of acute poisoning with nerve agents. We have therefore briefly mentioned it in this manuscript in the discussion relating to auto-injectors.
Reviewer
Benzodiazepine - these doses seem aimed at adults, and the doses of lorazepam are significantly more potent that those recommended for diazepam - is this the authors

intention? I suspect that they have followed manufacturers guidance which delivers a far more potent dose of benzodiazepine with lorazepam.

Authors

The doses listed in this paper are commonly used adult doses and have no relation to the manufacturer's recommendations. I have added pediatric doses based on The Harriet Lane Handbook, which is probably the most widely used pediatric reference manual in the US (Harriet Lane Handbook, 17th ed., Roberts J, Shilkofski N., ed. Mosby-Elsevier, Philadelphia, 2005) lists the following drug doses for seizures:
Lorazepam: 0.05-0.1 mg/kg/dose
Midazolam: 0.05-0.1 mg/kg/dose
Diazepam: 0.2-0.5 mg/kg/dose to max 5 mg (5 years of age)
or 10 mg for older children
Published pediatric reviews for seizures from nerve
agents use similar doses:
Lorazepam: 0.05-0.1 mg/kg/dose
Midazolam: 0.15-0.2 mg/kg/dose
Diazepam: 0.05-0.3 mg/kg/dose to max (5 years of age) or 10 mg for older children
(Rotenberg JS, Newmark J. Nerve Agents Attacks on Children: Diagnosis and Management. Pediatrics 2003;112:
648)

Reviewer

Decontamination - are the authors really proposing gastric lavage before activated charcoal? My understanding is that preliminary results from the large Sri Lankan study have not demonstrated any efficacy from lavage, and I certainly wouldn't recommend it, though I might consider gastric aspiration if I could control the airway. I would strongly suggest that gastric lavage is removed from this entry because I think there is no evidence of efficacy in significant overdose and potential for harm in this patient population, particularly from aspiration. Most patients with larger ingestion vomit. If it is included my firm recommendation would be to change the grading to Harmful.

Authors

Regarding the order of gastric lavage vs activated charcoal, there seems little rationale in administering charcoal prior to the lavage ince it will then be subsequently removed, and re-dosing would then be necessary.
Regarding the role of gastric lavage, we agree it is a controversial topic, and our personal practice is similar to that suggested by Professor Bateman. We agree there is no evidence of efficacy, so it was given the 'UE' designation. While we would in general be happy to discourage readers from conducting gastric lavage (eg. stating the procedure to be harmful), we are not confident that there is sufficient evidence in the literature at present to make this statement, and we would like to explain our reasoning as follows. We are not averse to changing the evidence recommendation to 'LIH' or 'UB' if this is the consensus.
Regarding the potential for harm, we agree that this is an important consideration. The data from Sri Lanka, if we understand the above reference correctly, refers to a small uncontrolled cohort of patients from the larger observational study. The method of performing gastric lavage represented by this data reflects a practice that is not widespread (to our knowledge), nor recommended – forced gastric lavage using an

orogastric tube in a patient who is restrained at four points on their back in the absence of sedation or a protected airway. For contrast, in North India where a gastric aspirate is required for legal purposes, recent data from a prospective study in ~100 patients with OP poisoning demonstrated a lack of adverse effects from their practice, which generally involves protection of the airway and careful monitoring.
In China, it is also considered a useful treatment such that an RCT to assess the efficacy of once vs thrice gastric washouts is planned.
Therefore, in the absence of data to adequately determine efficacy, and the above discussion regarding potential for harm and the perspective of clinicians in many Asian countries, we feel it should be mentioned in this review. However, we qualify this by stating that it only be considered in patients who present within 1-2 hours (it is likely that time to treatment will strongly influence the potential efficacy) and have a protected airway. We have added to this statement that a single aspiration of the gastric contents may be as useful as lavage.

Reviewer

I found box 5 rather difficult because most of what is here isn't really discussed in the text. If box 5 is going to be included, and one could make a strong case for excluding it from a review aimed at the generalist, then it must have some discussion of associated with it to try and put these various treatments in context. It is rather hard to discuss a treatment which has been shown to be efficacious in animals (organophosphorus hydrolases) with some of the other treatments suggested, such as extracorporeal "blood purification" whatever that may be. I presume the authors are referring to charcoal column perfusion, but I am not certain from this description.

Authors

The guidelines provided by BMJ requested for a box which inform readers of upcoming treatments and current research so we described this information in Box 5. This would allow interested parties to read other references for more information, if this was an interest to them (for example Reference 24). We comment at the top of this Box, and also in the text, that given the limited evidence that they are not currently recommended for routine use.
Extracorporeal blood purification is a widely used term which is intended to collectively include treatments such as haemodialysis, haemofiltration, haemoperfusion, plasmapheresis, etc. We have now listed the first three (most commonly used) treatments in Box 5 for clarification in case other readers are also confused by the term.

Reviewer

Figure 2 - minor toxicity lines. My view is that minor toxicity is very different to what is being described here, and what the authors are discussing are cases that have significant ingestion of organophosphates, not the usual case in Western societies, where you have delayed onset toxicity and therefore their presentation is of a moderate degree of toxicity in terms of symptoms. The word minor is really giving the wrong message. This is moderate to me . Figure 2 is a two-armed decision tree which provides the opportunity for patients to change between the clinical classifications if required. This comment appears to relate to the nomenclature of "minor toxicity" rather than its diagnosis or treatment. The patients included in this group are largely asymptomatic, and those who report possible effects may actually be suffering from the effects of the solvent or anxiety. We don't know believe the symptoms can be described as moderate.

In someone with minor toxicity can the authors explain the reason to do regular cholinesterase measurements? I don't know of any hospital in the UK that would have these available in a time-frame sufficient to influence treatment.

Authors

We have not recommended regular cholinesterase measurements in the manuscript. Suggestions for assessment and management are on the basis of clinical criteria. However, in the event that cholinesterase assays are available, we suggest that one may be obtained, and guidelines for interpretation of this are given.

Reviewer

In the UK information on management of this poisoning would of course be available via the National Poisons Information Service, this should be one of the resources listed in table 5, and reference to TOXBASE added please.

Authors

This table was included as per the BMJ 'instructions for authors', and is limited to resources available on the internet. Since TOXBASE and some other internet resources are not free to all users, they were not included in this table initially. We have now included reference to TOXBASE in Table 5, as requested, as well as other internet resources which require registration/payment for certain individuals. We have also clarified the role of the local poisons information centre as a means to access a clinical toxicologist (if one is available).

Reviewer 2, Dr I R Edwards, Director, WHO-UMC

I appreciate Dr. Edwards comments regarding our manuscript. We have read each comment carefully and where required, have responded below. We have made corresponding changes in the manuscript as attached. However, Dr. Edwards may not be aware of the BMJ emphasis on directing this to the generalist, and other instructions to stick with basics, and to avoid unnecessary controversy. I also think that he is unaware of the length restrictions and the instructions to use boxes and charts to convey much of the information.

Reviewer

This review is sound, but I have difficculties in relationship to its potential readership. I do not think that there is anything new here for those that treat OP poisoning regularly, and that the current research that may solve some of the continuing controversies is only dealt with superficially. I therefore take the view, in considering this paper, that the main aim is give guidance to those who may see an occasional case.

Authors

I agree with Dr. Edwards in that there is little new here for a practicing toxicologist. However, the emphasis of this article is towards the physician in general practice. By definition, this physician will see very few of these patients. We did not spend time on the continuing controversies as we wanted to cover the general approach, assessment and care of the acutely OP poisoned patient for someone who is unfamiliar with the exposure. The continuing controversies would serve as a point of confusion; we tried to stick with the general, evidence-based accepted management protocols.

Reviewer

Taking such a view, I find the diagnostic section is rather weak for prctical guidance. It really depends on reference to a box containing a list of symptoms and to a flow diagram.

Authors

There is very limited space available for this article. The guidelines provided by BMJ recommend the use of charts and boxes listing the key items as a way of providing the information in the most space-efficient manner.

Reviewer

The differential diagnosis is mentioned in the text, and I think the section on carbamates should be included there.

Authors

I have added carbamates to the differential diagnosis. We are reluctant to move the entire carbamate section to the differential diagnosis section because it introduces concepts not yet covered in the body of the article.

Reviewer

It would be a very good idea to add a table on the various common OPs and their characteristics in relationship to the appearance of signs and symptoms, and to their management.

Authors

I am adding a table on specific signs and symptoms with the recommended treatment. We have reservations with this idea of Dr Edwards because we believe strongly that this poisoning represents a continuum and as such, cannot be broken down into discrete separate steps and such a table will distract the reader from the more important clinical endpoints. As most generalists have never seen an organophosphate intoxication and confuse cholinergic with anticholinergic presentations, adding more confusion with the subtle differences between OPs would be counterproductive. Knowledge of individual differences does not influence management markedly when the decision tree that we have included is followed. Further, reliable data for an accurate description of the differences between the various OPs is unavailable. The only paper which has adequately described this difference (referenced in our review, Eddleston et al. Lancet 2005; 366: 1452-9) limited discussion to chlorpyrifos, dimethoate and fenthion. These OPs may not be as widely available and there is limited information on how other OPs differ so we do not consider this topic to be a priority in this review.

Reviewer

The flow diagram bifurcates after mentioning resuscitation. This is illogical when one branch is linked to minor exposure. There should be a prior step of evaluation.

Authors

Comment noted. However, whenever a patient presents to the physician, even with minor appearing signs and symptoms, triage as a form of assessment and resuscitation are inseparable.

“Resuscitation (assessment and management of airway, breathing, circulation) and targeted clinical review (Box 3) [LB]”

Included in this box is “targeted clinical review” which evaluates the patient and places him/her in minor or moderate/severe categories. The two authors are trained in emergency medicine where we look at all patients, assess and evaluate simultaneously (triage) in conjunction with resuscitation.

Reviewer

The important branch on the management of serious cases, I think fails to emphasize the importance of the level of consciousness and how those levels may be assessed.

Authors

Added to flow chart. We are reluctant to add Glascow Coma Scale as a measure of level of consciousness because the GCS was developed for head injuries and has not been validated in the case of acute OP poisoning.

Reviewer

The importance of respiratory capacity should also include how that is assessed.

Authors

Added to flow chart.

Reviewer

Fasciculations are of much less importance in determining severity since there is no quantification possible (there is a normal level of minor fasciculation possible).

Authors

We agree, and for this reason fasciculations were not recommended as clinical criteria for determining the severity of poisoning. We agree that there is no way to truly quantify fasciculations, but when present fasciculations may assist with the diagnosis of OP poisoning. For example, if I have a patient with miosis, mental status changes, and bradycardia, I include opioid or clonidine intoxication in my differential diagnosis. Since neither of these two cause fasciculations, but if this patient has fasciculations, it distinctly changes my diagnosis.

Reviewer

It really is important to emphasize the cases which need urgent, specialist attention, including need for care during transport.

Authors

Added to body of text.

Reviewer

There is no mention of acute-on-chronic poisoning in the occupational setting. In developing countries and in agricultural communities such cases are common. They present a diagnostic challenge, particularly in relationship to an apparently low level of acute dermal exposure.

Authors

This article is devoted to the assessment and treatment of acute poisonings.

Reviewer

In the management area, the guidance in the boxes is good, but there are some important issues missing. The use of AChE and BChE is dealt with but in two sections, the second seems to modify the advice in the first and they should be put together as a coherent section on the use of laboratory results.

Authors

This section has been combined.

Reviewer

Again the issue of acute-on-chronic exposure should be mentioned, when careful dermal decontamination is important.

Authors

This paper is only for acute exposures. Clothing removal as the first part of decontamination has been added to the initial assessment and management of these patients. However, dermal decontamination should not delay initial assessment and resuscitation.

Reviewer

Patients who relapse soon after treatment deserve special mention bearing in mind those who may be discharged from medical supervision soon after apparent cure. The re-use of contaminated clothing by workers has resulted in relapses after return to work soon after treatment. This should be mentioned.

Authors

Disposal of clothing has been added to the decontamination.

Reviewer

The management of atropine use is discussed, but perhaps more should be said about the most reliable criteria to use in titration, and the need for frequent, not just regular, clinical monitoring. I am not over impressed by the use of axillary dryness as a useful guide, for example. Heart rate and pupil size are much more practical.

Authors

Box 4 lists the end-points of atropinization as HR > 80 bpm and clear chest on auscultation. I have added resolution of bronchorrhea. Other criteria such as pupillary size are not clinically useful in titration. I agree and have deleted axillary dryness.

Reviewer

A minor point. The controversies of how oximes should be used could be described more clearly and the likely value of the large Asian studies in resolving some of these. There is a current article deriving from one of these studies, together with an editorial, to which they might refer.

Authors

We have reviewed this data and had included recent review papers which discuss this important issue (Eddleston et al, Clin Evidence 2006 & Buckley et al, Cochrane Library 2005) and a recent RCT (Pawar et al Lancet 2006; 368: 2136-41) in our references. In 2005 the South Asian Clinical Toxicology Research Collaboration hosted a workshop on pesticide poisoning which was attended by many clinicians in the Asia-Pacific region, and other countries. In general it was felt at this meeting that high doses of PAM were preferred. However, this is still an area of controversy and the data seems to suggest that when oximes are used, higher doses are better than lower doses. There are no validated dosing regimens. At this time, we feel that the WHO protocol (~12 gm/day), is a reasonable compromise between the very high dose (24 gm/day) from the Pawar study and the low dose used in a number of other papers (2-4 gm/day).

Reviewer

In summary, this has value for clinicians who are not experts and it should be strengthened with more detailed practical information relating to primary care clinical decisions, particularly in resource poor settings.

Authors

I am not sure what additional practical information should be added here. The primary focus of this article is basic assessment and management of acute organophosphorous insecticide intoxications for generalists. We have tried to provide a brief, concise précis conveying this information within the BMJ guidelines. Dr. Roberts has spent significant time practicing in resource poor settings and most of his recommendations reflect this. Although most of my practice is in first world resource-available environs, I too have had experience in resource poor settings. Since we recognize that laboratory assays may be difficult to obtain in a timely fashion, our endpoints for treatment are all based on clinical observations. As this manuscript is supposed to reflect state of the art evidence-based

information, we had to discuss treatment with the currently accepted antidotes. Atropine is almost universally available. Pralidoxime, obidoxime, or trimedoxime, although limited in quantity, should be available in the majority of locales where this article will be accessed. Both of us feel that appropriate treatment of OP poisoned patients should include an oxime so the article is written as such, but we have mentioned that the evidence supporting this is limited and that more research is in progress. We are restricted by manuscript length from providing detailed information which can be obtained from the reference list.