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Is oxygen required before atropine administration in organophosphorus or carbamate pesticide poisoning? – A cohort study

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Background. Early and adequate atropine administration in organophosphorus (OP) or carbamate insecticide poisoning improves outcome. However, some authors advise that oxygen must be given before atropine due to the risk of inducing ventricular dysrhythmias in hypoxic patients. Because oxygen is frequently unavailable in district hospitals of rural Asia, where the majority of patients with insecticide poisoning present, this guidance has significant implications for patient care. The published evidence for this advice is weak. We therefore performed a patient cohort analysis to look for early cardiac deaths in patients poisoned by anticholinesterase pesticides. *Methods.* We analysed a prospective Sri Lankan cohort of OP or carbamate-poisoned patients treated with early atropine without the benefit of oxygen for evidence of early deaths. The incidence of fatal primary cardiac arrests within 3 h of admission was used as a sensitive (but non-specific) marker of possible ventricular dysrhythmias. *Results.* The cohort consisted of 1957 patients. The incidence of a primary cardiac death within 3 h of atropine administration was 4 (0.2%) of 1957 patients. The majority of deaths occurred at a later time point from respiratory complications of poisoning. *Conclusion.* We found no evidence of a high number of early deaths in an observational study of 1957 patients routinely given atropine before oxygen that might support guidance that oxygen must be given before atropine. The published literature indicates that early and rapid administration of atropine during resuscitation is life-saving. Therefore, whether oxygen is available or not, early atropinisation of OP- and carbamate-poisoned patients should be performed.

Keywords Atropine; Oxygen; Organophosphorus; Carbamate; Ventricular dysrhythmia

Introduction

Pesticide self-poisoning is a major global clinical problem, killing an estimated 350,000 people every year.[1–3] The World Health Organization (WHO) has identified pesticide poisoning as the single most common method of suicide worldwide.[4,5] Organophosphorus (OP) insecticides are the most important pesticides and act through phosphorylating the active site of cholinesterases, resulting in acetylcholine build-up.[6,7] This produces excessive cholinergic stimulation, causing clinical features in both the peripheral and central nervous systems. Carbamate insecticides are also important and produce similar effects.

Despite the widespread incidence of OP and carbamate insecticide poisoning, there has been little agreement about the best treatment.[8,9] Therapy involves resuscitation including administration of oxygen and fluids, support for airway and ventilation, a muscarinic antagonist (usually atropine) and, for OP poisoning, an acetylcholinesterase reactivator (usually pralidoxime or obidoxime).[10,11] Atropine and oximes were introduced into clinical practice without clinical trials to guide their use; therefore, the best way of using these drugs is still under study.

A recent trial from Bangladesh[12] showed markedly more rapid atropinisation of OP-poisoned patients with a doubling dose regimen[13] of atropine rather than a standard bolus dose regimen.[8] The time to stabilisation was reduced from a mean of 152 min (95% CI: 130–173) to 24 min (95% CI: 20–28) ($P < 0.001$) in those receiving the doubling regimen; this faster stabilisation was associated with a mortality reduction from 22.5% to 8% ($P = 0.01$). This study demonstrates a clear clinical benefit achieved by administering atropine rapidly to sick patients with anticholinesterase insecticide poisoning.

However, such rapid administration of atropine is hindered by textbooks and articles stating that oxygen must be given prior to atropine due to the risk of atropine-induced ventricular tachycardia or fibrillation (Box 1). District hospitals in rural Asia, which deal with the vast majority of anticholinesterase poisoned patients, are often understaffed and inadequately equipped.[14] Many of the these hospitals do not have

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Box 1. Quotes from articles stating the need for oxygen prior to atropine in OP pesticide poisoning

'Atropine must not be given until oxygenation is adequate, or ventricular fibrillation may occur.'[30]

'Improve tissue oxygenation as much as possible before administering atropine, so as to minimize the risk of ventricular fibrillation'[39,61]

'In order to obviate the added risk of hypoxia-induced ventricular dysrhythmias, correct cyanosis before administering atropine'[15]

'Adequate oxygenation is important as atropine can precipitate ventricular fibrillation in the presence of hypoxia'[19]

'Supplemental oxygen should be given, ideally before atropine administration, as hypoxia may increase the risk of atropine-induced dysrhythmias'[34]

easy access to oxygen and this practice therefore causes a delay in administering atropine or for atropine to be withheld. This delay will result in prolonged hazardous cholinergic effects such as bronchospasm, bronchorrhoea, bradycardia and hypotension, risking the patient's life (Box 2).

In a literature review, we found 28 publications (14 textbooks and 14 papers) published between 1959 and 2012 that stated atropine (i) should not be given before oxygen[7,15–31] or (ii) should ideally not be given before oxygen due to the risk of it causing ventricular dysrhythmias in hypoxic OP pesticide-poisoned patients.[32–41] However, on inspection, only 2 of the 28 papers provided any evidence of ventricular dysrhythmias after atropine administration[32,41] (Box 3), and neither offered even modest evidence of an association. The majority of articles provided this guidance without any reference to the literature (Fig. 1).

Box 2. Consequences of not giving atropine when oxygen is unavailable

Kecik and colleagues reported the case of a 17-year-old woman with acute severe self-poisoning with the OP insecticide dichlorvos.[26] She was transferred to the local hospital 1 h post ingestion and there received atropine (48 mg) and pralidoxime. Thirty-six hours later her condition deteriorated and she was transferred to the intensive care unit of a second hospital. On admission, she showed marked cholinergic signs (sweat, bronchorrhoea, cyanosis, tachypnoea, confusion, and paralysis). However, atropine was withheld due to a lack of oxygen and the belief that its administration would result in ventricular fibrillation. The patient remained hypoxic for 3 days and unconscious for 8 days. She ultimately survived to hospital discharge on Day 31, despite receiving no atropine during her hospital admission. Administration of atropine would likely have treated her cholinergic syndrome, allowing improvement in her oxygen saturation, consciousness and general condition.

Box 3. Details of the primary cases

Hase case[41]

Hase and colleagues reported the case of a 26-year-old man who was admitted to hospital after self-poisoning with the OP insecticide diazinon. He was hypoxic, bradycardic and had pulmonary oedema and was immediately intubated. He received atropine until atropinisation: 40 mg of atropine over 30 min. Ten minutes later, he became pulseless and ECG showed ventricular tachycardia, and then ventricular fibrillation. The patient recovered after receiving a DC shock. The authors reported that atropine decreases the threshold for ventricular tacharrhythmias, by lowering the vagal tone and increasing the heart rate.[51] They also hypothesised that hypoxia, bradycardia and pulmonary oedema further lowered this threshold.

Finkelstein cases[32]

This study included 53 patients with severe OP pesticide poisoning requiring ventilation and intensive care monitoring who were treated according to a standard protocol. Patients received atropine 2 mg IV at intervals of 10 min or more until bronchospasm and bronchorrhoea were controlled. Cyanotic or hypoxemic patients received short treatments of 100% oxygen, until an oxygen saturation of above 92% was confirmed, prior to each atropine dose. Despite this protocol, 22 (41.5%) developed cardiac arrhythmias (four [18%] had supraventricular arrhythmias; six [27%] had asymptomatic prolonged Q-T interval; four [18%] had asymptomatic ventricular premature beats; and eight [37%] had ventricular tachycardia and/or 'torsade de pointes'). Four patients with ventricular tachycardia and/or 'torsade de pointes' died, and in the other four, arrhythmia was successfully controlled by a temporary pacemaker. They concluded that 'atropine may induce cardiac arrhythmia if administered during hypoxemia',[32] despite the ineffectiveness of correcting hypoxia before atropine administration in their study.

The aim of this paper is to analyse the data derived from nearly 2000 Sri Lankan patients with OP or carbamate poisoning who routinely received atropine before oxygen to determine whether there is evidence of early cardiac deaths that might be due to atropinisation.

Materials and methods

Patient cohort

In order to examine the occurrence of fatal ventricular dysrhythmias after treatment with atropine, a database of all OP and carbamate pesticides-poisoned patients treated in Anuradhapura and Polonnaruwa district hospitals in Sri Lanka from 31 March 2002 to 1 September 2005 was examined. The cohort included two randomised controlled trials (RCT).[42–44] The first RCT compared multiple

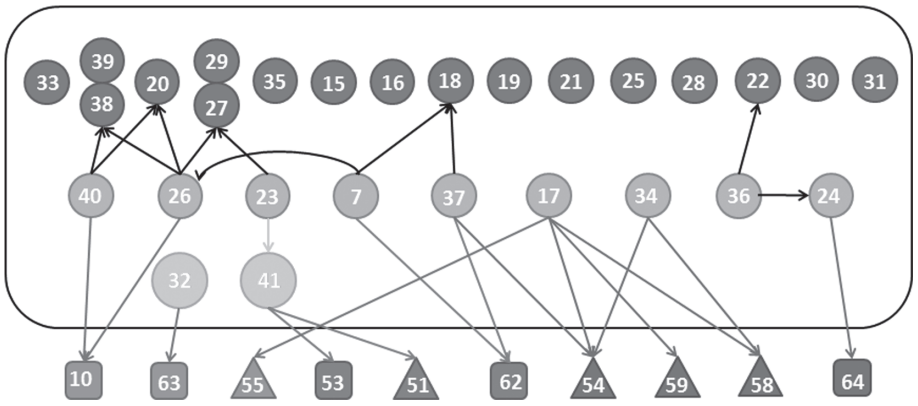

Fig. 1. Publications linked to the references they cite to underpin this guidance. *Circles* within the *black rectangle*: the 28 publications found to state this guidance. By colour: *blue*, without supporting citations; orange, provide non-relevant supporting citations; *green*, provide relevant supporting citations. Outside the *rectangle*, in *squares*, cited human publications that are not relevant: in *light blue*, primary OP pesticide papers; in *red*, primary cardiac disease papers; in *purple*, primary nerve agent papers. *Triangles*: animal studies. Numbers correspond with the references. Publications from the same book, with a different edition, are placed together (refs 27 and 29, and 38 and 39). Of the 28 publications, 11 cited a source for their statement while 17 did not provide any supporting evidence. The 11 publications cited 18 sources on 27 occasions. Eleven citations were to relevant but secondary sources[18,20,22,24,26,29,38] while seven citations were of irrelevant primary or secondary sources (patients with myocardial infarctions, nerve agent studies, or patients with pesticide poisoning but no ventricular dysrhythmias[10,53,62–64]). Animal studies with OP nerve agents, pesticide active ingredients, or myocardial infarctions[51,54,55,58,59] were cited on eight occasions (colour version of this figure can be found in the online version at www.informahealthcare.com/ctx).

dose with single dose or no charcoal in all self-poisoned patients between 31 March 2002 and 16 Oct 2004.[43] The second RCT was conducted in Anuradhapura and Polonnaruwa district hospitals from 26 May 2004 until 18 October 2006 to compare pralidoxime with placebo, in addition to standard therapy, in symptomatic OP pesticide poisoning.[44]

IRB approval for the studies was received from the Faculty of Medicine Ethics Committee, Colombo, and Oxfordshire Clinical Research Ethics Committee, UK.

Treatment and procedure

Patients were resuscitated following standard protocols, including evaluation of airway breathing and circulation.[13] Due to the absence of emergency departments at the time of the study in the study hospitals, patients first received medical care on arrival at the medical ward. This typically delayed initial treatment by 10 min. Oxygen was not immediately available at any site of resuscitation.

Conscious patients with cholinergic signs (especially miosis, sweating, ref 13) were given an initial dose of 0.6–1.2 mg of atropine rapidly IV; unconscious patients were treated with an initial dose of atropine 1.8–3 mg. If after 5 min atropinisation had not occurred, a double dose was given. This doubling was continued each time that there was no response (improved heart rate and blood pressure, clear lungs). Because oxygen was rarely available on the ward and had to be brought from intensive care, protocols did not require the administration of oxygen before atropine since this would delay treatment.

Once stable, patients received activated charcoal as per their allocation during the RCT.[43] No patients in this cohort received forced emesis; patients presenting within 1 h of a potentially lethal ingestion who provided consent underwent gastric lavage.

Patients were resuscitated with fluids to ensure adequate fluid output and ventilated as necessary. Symptomatic patients also received 1 g of pralidoxime chloride every 6 h for 1–3 days or, if they were recruited to the pralidoxime RCT, they received either placebo or 2 g of pralidoxime chloride over 20 min followed by 0.5 g/hr until death, they had no further need for atropine, or 7 days.[44] Sick patients were placed on a cardiac monitor (including oxygen saturation monitoring) for several hours after arrival in the ward; due to a lack of intensive care beds, the majority of patients were managed on the open ward for the first few hours to days. Temporary pacemakers were not used for these patients.

Patients were seen by study doctors soon after their admission to the medical ward, frequently while unstable in the first few hours, and then twice daily on ward rounds. They were also called to see the patient whether any events occurred. Events, such as endotracheal intubation, seizures, cardiorespiratory arrests or death, were recorded at the time of the event and entered into a prospective database. We used the incidence of fatal primary cardiac arrests as a sensitive (but non-specific) marker of likely ventricular dysrhythmias.

Analysis

Administration of sufficient atropine to resuscitate and stabilise patients on admission in this series takes an estimated 23.4 mg (range: 1–75) of atropine within half an hour.[8] The recent Bangladeshi trial reported a mean time of 24 min (95% CI: 20–28) for this regimen in 69 patients. We hypothesised that atropine-induced dysrhythmias would likely occur within the first hour of atropine administration. To be conservative we therefore looked for any OP or carbamate pesticide patients dying from a primary cardiac arrest within 3 h of admission. If atropine-induced ventricular dysrhythmias are a serious problem, we would expect to see evidence of such deaths.

We examined the database for deaths of OP and carbamate insecticide-poisoned patients and plotted the time from admission to death. We then identified those patients who died from a respiratory or cardiac arrest, plotting for the latter group the interval from admission to death. Because some patients had cardiac arrests following respiratory arrests, we classified primary cardiac arrests as occurring more than 2 h after any respiratory arrest.

The analysis included all patients who presented to the two study secondary hospitals. None were transferred out to other hospitals. Many patients were transferred from surrounding primary hospitals where symptomatic patients would have received atropine.

Statistics

The primary data analysis was performed in GraphPad Prism (version 5). Demographic factors and clinical characteristics were summarised using counts (percentages) for categorical variables and the median [interquatile range (IQR)] for non-normally distributed continues variables.

Results

The database contained details of 1957 patients with OP and carbamate pesticide poisoning admitted to hospital between 31 March 2002 and 1 September 2005. Out of these patients, 49.7% were transferred from surrounding peripheral hospitals after administration of atropine.

In total 222 (11.3%) patients died. Eight were excluded from the analysis because they died on arrival in the ward, before atropine could be given. Cardiac arrest was recorded, most often in combination with a respiratory arrest, for 136 patients. Fifty-five had a primary cardiac arrest as cause of death. Baseline demographic and clinical characteristics of all patients who died and those dying from primary cardiac arrests are presented in Table 1.

For all 214 deaths of OP and carbamate-poisoned patients receiving atropine, 22 (10.3%) occurred within the first 3 h (22/1957, 1.1%; Fig. 2, Table 2). Only six occurred within the first hour and half of these were due to dimethoate-induced distributive cardiovascular shock.[45] Of the 55 primary cardiovascular deaths, only 1 (1.8%) occurred within the first hour and 4 occurred within the first 3 hours (7.3%). The incidence for a primary cardiac death within 3 h of atropine administration, and thereby an estimate for the maximum rate of fatal ventricular arrhythmia, was 4/1957 (0.2%).

Discussion

The weak published evidence for atropine-induced ventricular dysrhythmias in anticholinesterase poisoning is supported by our analysis of the largest cohort of OP and carbamate-poisoned patients published. In this Sri Lankan cohort, routinely treated with atropine before oxygen, the incidence of death from cardiac arrest during the first 3 hours of hospital admission was 0.2%. It is possible that the actual incidence of (non-fatal) ventricular dysrhythmias was higher than this; however, the data indicate that serious atropine-induced dysrhythmias are not a major clinical problem.

The common advice that oxygen should be given before atropine after OP poisoning due to the risk of ventricular dysrhythmias is based upon a single case report. This lack of evidence is startling in the face of the estimated two mil-

Table 1. Baseline demographic and clinical characteristics of all patients who died and patients who died with a primary cardiac arrest.

	All causes of death	Primary cardiac arrest
Number	214	55
Demographic characteristics		
Age, y, median (IQR)	42 (31–52)	42 (30–54)
Males (%)	183 (85.5)	47 (85.5)
Time from ingestion to admission, h, median (IQR)	3 (2–5)	3 (2–4)
Admission characteristics		
Symptomatic (%)	190 (88.8)	49 (89.1)
GSC score, median (IQR)	6 (3–13)	3 (3–12)
Treatment		
Previous atropine (%)	131 (61.2)	36 (65.5)
Oxime treatment (%)	155 (75.6)	43 (78.2)
Intubated (%)	183 (85.5)	50 (90.9)
Poisoning		
Chlorpyrifos (%)	47 (22.0)	13 (23.6)
Dimethoate (%)	81 (37.9)	22 (40.0)
Fenthion (%)	16 (7.5)	5 (9.1)
Other OP insecticide* (%)	28 (13.1)	5 (9.1)
Carbamate insecticide† (%)	15 (7.0)	3 (5.5)
Unknown anticholinesterase insecticide (%)	27 (12.6)	7 (12.7)

IQR, interquartile range. Data are number (%) or otherwise indicated. Data were collected on admission to hospital; recruitment occurred soon after.

*Other OP insecticides included: diazinon, malathion, oxydemeton-methyl, phenthoate, profenofos, prothiofos, and quinalphos.

†Carbamates included: carbosulfan and fenobucarb.

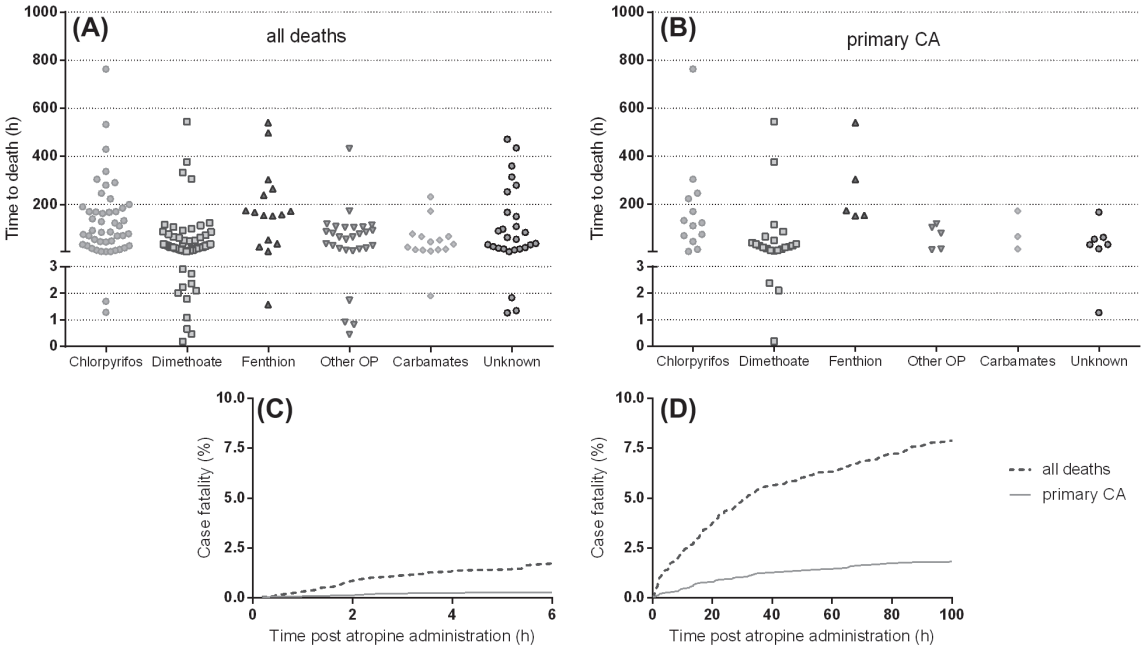

Fig. 2. Plot of time from admission to death for each patient (A and B) and cumulative percentage of death post admission (C and D). A: patients with any cause of death. B: patients dying from a primary cardiac arrest. See Table 1 legend for a list of other OP insecticides. Cumulative percentage of patients who died with any cause of death (*broken blue*), and patients dying from a primary cardiac arrest (*solid red*). C: up to 6 h post atropine administration; D: up to 100 h post atropine administration (colour version of this figure can be found in the online version at www.informahealthcare.com/ctx).

lion cases of OP or carbamate poisoning that have occurred each year for the last 20–30 years. The majority of articles offering this guidance appear to have made it without any reference to the literature, resulting in the guidance being copied from article to article, review to review.

Sadeeh,[46] Karki,[47] and colleagues studied the cardiac and electrocardiographic manifestations of acute OP poisoning in two case series. They reported that hypoxaemia, electrolyte derangements, and acidosis were predisposing factors for the development of cardiac complications. However, neither study found a correlation between administration of high doses of atropine and ventricular dysrhythmias. Of note, the first ECGs were usually taken before resuscitation and administration of oxygen or atropine, causing a delay in atropine administration that was likely hazardous to patients and ethically questionable. Ludomirsky[37] studied the occurrence of Q-T prolongation and torsade de pointes in OP pesticide-poisoned patients, reporting Q-T prolongation in 14 of 15 cases and 6 tachydysrhythmias. However, these dysrhythmias were unrelated to the use of atropine.

Rapid administration of atropine can be life-saving.[12] The evidence reported here indicates that its administration should not be held back by the lack of oxygen therapy, since atropine will reduce fluid in the lungs and improve oxygenisation[45] as well as treat hypotension and bradycardia. We recommend that oxygen is provided as soon as possible to all moderate-to-severely poisoned patients but that its absence does not slow or prevent the provision of atropine. This guidance was already given by Fernando in 1989[35] and was implicit in the key review published by Namba in 1971.[10] It has become more commonplace over the last few years.[48,49]

The recommendation for provision of oxygen before atropine has been in the cardiology literature since the 1970s. There is evidence to show that atropine can have adverse effect in patients following cardiac complications such as myocardial infarction.[50–53] However, we have been unable to find any discussion comparing the focal ischaemia found in myocardial infarction with the global ischaemia found in pesticide poisoning. The relevance of these data to young previously fit patients with normal hearts and anticholinesterase poisoning seems less certain.

Contrary to the very limited human data, five animal studies have been published. However, only two looked at pesticide poisoning[54,55] and these were with unformulated TEPP

Table 2. Time of death since admission for OP or carbamate-poisoned patients treated with atropine.

	All causes of deaths	Primary cardiac arrest
Time to death since admission, h, median (IQR)	36 (14–111)	55 (14–152)
Time of death using categorical variable		
<3 h	22 (10.3)	4 (7.3)
3–100 h	132 (61.7)	31 (56.4)
>100 h	60 (28.0)	20 (36.4)

IQR, interquartile range.
Data are number (%) or otherwise indicated.

and parathion active ingredients (rather than the formulated agricultural pesticides that people ingest[56]). Three studied dysrhythmias after atropine treatment in OP nerve agent poisoning.[57–59] Ventricular dysrhythmias only occurred in dogs and not in other species. In response Hayes stated: 'the fact that no reports of cases of sudden death following administration of atropine have been found indicates that there may be a marked species difference so that the danger of giving atropine in the presence of cyanosis in human cases is small or simply that few, if any, patients have the degree of cyanosis involved in the animal studies.'[60]

Limitations

This prospective dataset documented only whether and when a patient had had a cardiac arrest or respiratory arrest. Resources were limited in the hospitals and patients were rarely treated in an intensive care unit where continual cardiac monitoring and observation could take place. However, initial atropinisation was done by a research team with sick patients on a cardiac monitor so dysrhythmias would have been noted in these early stages. No patients were reported to die from ventricular dysrhythmias and there was no sense that atropine administration was hazardous in the absence of oxygen.

Many of the patients were transferred from peripheral hospitals where they had received atropine. This would have improved the clinical condition of some patients and reduced the risk of complications. However, all patients were assessed during resuscitation at the secondary hospitals for cholinergic signs and the majority required atropine. The analysis does not include patients who died between presentation at the primary hospital and arrival in the medical wards of the study secondary hospital.

Conclusion

Adequate atropinisation is key for the management of OP and carbamate poisoning and should be done early, with appropriate titration and monitoring of developing adverse events. Currently, we can find no evidence to support the claim that oxygen must be given before atropine. It is likely that in hospitals where oxygen is not available, early administration of atropine during resuscitation is life-saving.[12] Guidelines for management of OP and carbamate poisoning should recommend early atropinisation of patients, whether oxygen is available or not.

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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