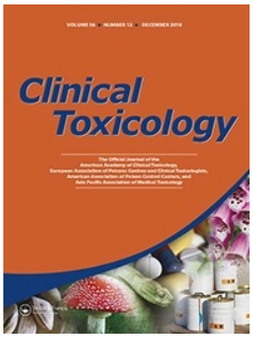


Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

Adrenaline is effective in reversing the inadequate heart rate response in atropine treated organophosphorus and carbamate poisoning

Abhishek Samprathi , Binila Chacko , Shilpa Reynal D'sa , Grace Rebekah , C. Vignesh Kumar , Mohammad Sadiq , Punitha Victor , John Prasad , Jonathan Arul Jeevan Jayakaran & John Victor Peter

To cite this article: Abhishek Samprathi , Binila Chacko , Shilpa Reynal D'sa , Grace Rebekah , C. Vignesh Kumar , Mohammad Sadiq , Punitha Victor , John Prasad , Jonathan Arul Jeevan Jayakaran & John Victor Peter (2020): Adrenaline is effective in reversing the inadequate heart rate response in atropine treated organophosphorus and carbamate poisoning, Clinical Toxicology, DOI: 10.1080/15563650.2020.1836376

To link to this article: https://doi.org/10.1080/15563650.2020.1836376

Published online: 02 Nov 2020.

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2020.1836376

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

Adrenaline is effective in reversing the inadequate heart rate response in atropine treated organophosphorus and carbamate poisoning

Abhishek Samprathi[a], Binila Chacko[a], Shilpa Reynal D'sa[a], Grace Rebekah[b], C. Vignesh Kumar[c], Mohammad Sadiq[c,d], Punitha Victor[c], John Prasad[c], Jonathan Arul Jeevan Jayakaran[c] and John Victor Peter[a]

[a]Medical Intensive Care Unit, Christian Medical College, Vellore, India; [b]Department of Biostatistics, Christian Medical College, Vellore, India; [c]Department of Medicine, Christian Medical College, Vellore, India; [d]Speciality Registrar, Edinburgh Center for Endocrinology and Diabetes, NHS, Edinburgh, UK

ABSTRACT

Background: In acute organophosphorus (OP) or carbamate poisoning, some patients require high dose atropine to counteract the effects on heart rate (HR) and blood pressure (BP). This study describes the factors associated with high dose atropine therapy and the use of adrenaline to reverse the inadequate HR response to atropine.

Methods: Consecutive patients admitted to the intensive care unit (ICU) were prospectively recruited. Demographic data, treatment and outcomes of patients who failed to achieve target HR (100/min) or systolic BP >90 mm Hg with either a cumulative atropine dose of 100-mg within 6-h following admission or an infusion of 30 mg/h for at least 3-h were compared with patients who achieved the targets. Factors associated with high dose atropine therapy were explored using logistic regression analysis and expressed as odds ratio (OR) with 95% confidence intervals (CIs).

Results: Of the 181 patients admitted with OP or carbamate poisoning, 155 patients fulfilled inclusion criteria. The mean (SD) age was 35.7 (15.8) years; admission APACHE-II score was 14.6 (7.5). Heart rate and/or BP target was not achieved in 13.6%. In these patients, target HR was achieved after adding adrenaline infusion at 2–4 μg/min. Ventilation duration (11.6 ± 6.3 vs. 8.4 ± 6.9 days, $p = 0.05$) and ICU stay (12.3 ± 5.8 vs. 8.9 ± 5.8 days, $p = 0.01$) were longer in patients requiring high dose atropine when compared with others. On multivariate logistic regression analysis, shorter time to presentation to hospital ($p = 0.04$) was associated with need for high dose atropine. Overall mortality was 9% and similar in both groups ($p = 0.41$).

Conclusions: High dose atropine therapy is required in a subset of patients with OP and carbamate poisoning and was associated with longer ventilation duration and ICU stay. Adrenaline infusion improved hemodynamics in these patients.

ARTICLE HISTORY
Received 4 August 2020
Revised 6 October 2020
Accepted 6 October 2020

KEYWORDS
Poisoning; organophosphorus; carbamate; mortality; atropine; adrenaline

Introduction

Organophosphorus (OP) and carbamate poisoning are common in developing countries due to easy access and lack of restriction on the sale of pesticides. Toxicity is primarily due to acetylcholinesterase inhibition in the central and peripheral nervous systems, neuromuscular junction and erythrocytes, resulting in overstimulation of nicotinic and muscarinic receptors [1]. Atropine is the mainstay of treatment [2].

The dose of atropine needed to reverse the cholinergic signs is variable and often unpredictable. There are several protocols for atropinization and there is lack of consensus on a standard regime [3]. Two approaches are followed. Both rely on clinical features for atropinization. In one study, "conventional bolus dose treatment" was associated with delay in stabilization and higher mortality when compared with "incremental boluses followed by an atropine infusion" [4]. Since low heart rate (HR), low blood pressure (BP) and excessive secretions can increase morbidity, atropinization targets include an adequate BP, minimum HR and clear lung fields [4,5]. The dose of atropine is titrated to achieve these objectives.

Some patients fail to respond to standard doses of atropine and require escalating dose of atropine to achieve atropinization targets. These patients may manifest an inadequate HR response (<70/min) and/or persistently low systolic BP of <90 mm Hg despite reversal of other cholinergic signs like bronchorrhea and increased salivation. Bradycardia in this setting increases the risk of malignant arrhythmias [6]. High dose atropine on the other hand, can cause hyperthermia, psychosis, delirium, seizures or coma [7,8]. Literature on requirement of high dose atropine in OP poisoning is limited to case reports [9–11] and one small case series [12]. Given this background, this study evaluated the incidence and factors associated with the need for high dose atropine therapy in OP and carbamate poisoning and detailed the temporal course of atropine requirements in refractory patients pre- and post-treatment with low dose adrenaline infusion.

CONTACT John Victor Peter peterjohnvictor@yahoo.com.au Medical ICU, Christian Medical College, Vellore 632 004, India

Patients and methods

This prospective observational study was done over a 2-year period (2015–2017) in a tertiary care university affiliated teaching hospital in South India. All patients over 18 years of age, with a history of intentional ingestion of an OP or carbamate compound and presenting within 12 h of consumption were considered for inclusion. The compound was identified based on the canister brought by the patients' relatives at presentation, in patients with clinical evidence of muscarinic and nicotinic manifestations and biochemical evidence of suppression of butyrylcholinesterase activity (reference range 3000–8000 U/L). In situations where the compound was not identified, if patients manifested cholinergic symptoms and signs and had biochemical evidence of butyrylcholinesterase inhibition, they were classified as unknown compound ingestion. Biochemical assays were not done for compound identification.

Patients were treated with atropine and supportive care that included mechanical ventilation and other organ support as required. Oximes were not used [13]. Ventilated patients received analgo-sedation with morphine or fentanyl in combination with midazolam, titrated based on the sedation score. Sedation was ceased prior to extubation when ventilation was weaned.

A modified protocol of atropinization was followed [3]. The mandatory clinical targets for atropinization that were used in the study included (a) clear lung fields on auscultation (indicated by the absence of bronchorrhea, bronchospasm and increased salivation), (b) target HR >100/minute on day 1 and (c) systolic BP >90 mm Hg. The higher targets for HR and BP were based on prior experience of management of patients with severe poisoning and late presentations. Following atropinization, atropine infusion was titrated to maintain the above targets on day one. The target HR was reduced to >90/min on day two and >80/min on subsequent days. The other secondary targets for atropinization that were monitored routinely in these patients included pupils (aiming for mid-size pupils) and bowel sounds (bowel sounds being just present rather than absent).

Patients were considered to have received "high dose atropine therapy" if they failed to achieve target HR and/or a systolic BP of >90 mm Hg despite adequate fluid resuscitation in the setting of clear lung fields, with either a cumulative atropine dose of 100-mg within six hours of presentation or an infusion of 30 mg/h for at least three hours. Patients who were unresponsive to high dose atropine therapy, as defined above, were commenced on with low dose adrenaline infusion (2–4 μg/min) and the doses of atropine and adrenaline were titrated down as the target HR and BP were reached.

Demographic, treatment and outcome data were recorded. The primary outcome was the need for high dose atropine therapy, as defined above. Secondary outcomes included mortality, length of stay, need for ventilation and development of intermediate syndrome or delayed organophosphate encephalopathy. A diagnosis of delayed organophosphate encephalopathy was considered [14] if a patient developed an altered conscious state or coma after an initial period of normal consciousness of >72 h, after ruling out metabolic abnormalities, sedative drugs and cerebral pathology (e.g., hypoxic or traumatic brain injury, seizures) as a cause for altered consciousness.

Baseline characteristics were summarized as frequencies (percentages) for categorical variables and mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables as appropriate. *T*-test or Fisher's test was used to compare the baseline characteristics and outcome between patients who required high dose atropine and those who did not. Bivariate logistic regression analysis was done to explore the factors associated with the need for high dose atropine therapy as well as mortality. Factors identified ($p < 0.1$) on bivariate logistic regression analysis were incorporated in a multivariate logistic regression analysis to explore for factors independently associated with need for high dose atropine and death and expressed as odds ratio (OR) with 95% confidence intervals (CIs). All statistical analyses were done using STATA v15.0 (StataCorp, College Station, TX). The study was approved by the institutional review board (IRB) and ethics committees of the institution (IRB Min. No. 10100, dated 10 June 2016).

Results

During the study period, 181 patients were admitted with a presumptive diagnosis of OP or carbamate poisoning. Of these, 25 patients who presented after 12 h of ingestion and one patient with normal butyrylcholinesterase activity were excluded. Baseline characteristics are summarized in Table 1. The cohort was relatively young (mean (SD) age 35.7 ± 15.8 years) with a male preponderance (115:40) with moderate severity of illness (APACHE-II score 14.6 ± 7.5). The majority of poisoning was due to a diethyl (45.8%) or dimethyl compounds (27.7%); 3.9% had taken a carbamate compound.

High dose atropine was required in 21 patients (13.6%). These 21 patients manifested an inadequate HR response prior to initiation of adrenaline; two patients in addition had a systolic BP of <80 mm Hg. There was no difference in the baseline characteristics of patients who required high dose atropine and those who did not, except that the time to presentation was significantly shorter (4.1 ± 2.7 vs. 6.1 ± 3.9 h; $p = 0.03$) in those who required high dose therapy (Table 1). The main compounds that were implicated were monocrotophos (six patients), chlorpyrifos (three patients) and triazophos (three patients). No arrhythmias were noted in any patient during the study period.

On *post hoc* analysis, of the 21 patients who needed high dose atropine, 15 patients had a persistently inadequate HR response of ≤80/min while in six patients who had HR of >80/min at the time of initiation of adrenaline infusion, target HR was not achieved. In the six patients with an HR of >80/min, the mean (SD) atropine infusion rate was 25.7 (12.0) mg/h when adrenaline infusion was commenced and the cumulative atropine dose received prior to that was 177.7 (132.7) mg; in this subset of patients, the cumulative dose of atropine over the first five-days was 1102 (841) mg.

Table 1. Baseline characteristics and outcomes of the study group.

	All patients ($n = 155$)	Low dose atropine ($n = 134$)	High dose atropine ($n = 21$)	p Value
Baseline characteristics				
Age, years	35.7 (15.8)	34.5 (15.2)	43.3 (17.7)	.02
Gender, male:female	115:40	99:35	16:5	1.0
APACHE II score	14.6 (7.5)	14.2 (7.3)	16.9 (8.0)	.12
Type of compound[a]				
Dimethyl	43 (27.7)	36 (26.9)	7 (33.3)	.24
Diethyl	71 (45.8)	64 (47.8)	7 (33.3)	
S-alkyl	10 (6.5)	10 (7.4)	–	
Carbamate	6 (3.9)	4 (3.0)	2 (9.5)	
Unknown	25 (16.1)	20 (14.9)	5 (23.8)	
QTc[b] interval, ms	454 (35.1)	453 (32.0)	463 (49.4)	.23
Butyrylcholinesterase, U/L	336 (491)	346 (515)	269 (291)	.50
Lag time[c], h	5.8 (3.8)	6.1 (3.9)	4.1 (2.7)	.03
Outcomes				
ICU LOS, days	9.4 (5.9)	8.9 (5.8)	12.3 (5.8)	.01
Hospital LOS, days	14.6 (9.4)	14.2 (9.7)	16.9 (7.1)	.23
Number ventilated[a]	140 (90.3)	119 (88.8)	21 (100)	.23
Ventilation duration, days	8.9 (6.9)	8.4 (6.9)	11.6 (6.3)	.05
Intermediate syndrome[a]	65 (41.9)	52 (38.8)	13 (61.9)	.06
DOPE[a]	13 (8.4)	12 (9.0)	1 (4.8)	1.0
Mortality[a]	14 (9.0)	11 (8.2)	3 (14.3)	.41

APACHE: acute physiology, age, chronic health evaluation.
All values are mean (standard deviation) unless specified; p values indicate the comparisons between those who required high dose atropine therapy and those who did not.
[a]For these variables, values are number of patients and the percentages are in parentheses.
[b]Corrected QT interval on the admission ECG.
[c]Lag time from ingestion to presentation to hospital; ICU: intensive care unit; LOS: length of stay; DOPE: delayed organophosphate encephalopathy.

In the subset of 15 patients who had a persistently low HR response (HR $\leq$ 80/min) to atropine prior to adrenaline infusion, the mean atropine infusion rate was 19.9 (8.8) mg/h and the cumulative atropine dose was 144 (61.2) mg.

Patients requiring high dose atropine were treated with adrenaline infusion. Although the median requirement of adrenaline (Table 2) was between 2 and 4 μg/min, there was considerable individual variation in the dose required. The infusion rate ranged from a minimum of 0.5 μg/min and a maximum of 20 μg/min in the first hour after starting adrenaline infusion to a minimum of 0 μg/min and maximum of 12 μg/min at 6 h. Eight patients required adrenaline beyond 12 h (maximum dose 8 μg/min) and all patients were weaned off adrenaline within 24 h. Table 2 summarizes the hourly atropine infusion rate, HR and cumulative atropine dose over the six hours prior to initiating adrenaline and for the six hours post adrenaline. Atropine requirement plateaued following commencement of adrenaline infusion and the target HR was achieved within a couple of hours following initiation of adrenaline infusion and was sustained subsequently (Figure 1). The median (IQR) atropine requirement in the first five days of intensive care unit (ICU) stay was 748 mg (IQR 602–963 mg) in the group that needed high dose atropine and adrenaline infusion whereas it was 158 mg (IQR 67–293 mg) in the group that did not require high dose atropine (data available in 130 patients).

Patients who required high dose atropine had significantly longer duration of ventilation ($p = 0.05$) and stayed longer in the ICU ($p = 0.01$); however, hospital stay and mortality were similar. Intermediate syndrome tended to be more frequently observed ($p = 0.06$) in these patients (Table 1). On bivariate logistic regression analysis (Table 3), age ($p = 0.02$), shorter time to presentation to hospital ($p = 0.03$) and intermediate syndrome ($p = 0.05$) were associated with the need for high dose atropine. On multivariate logistic regression analysis, only shorter time to presentation to hospital was significant ($p = 0.04$).

Overall mortality was 9% (14/155). Age, severity of illness (APACHE-II score) and the development of delayed organophosphate encephalopathy [14,15] were associated with death on bivariate logistic regression analysis (Table 4). On multivariate logistic regression analysis, severity of illness and delayed organophosphate encephalopathy were independently associated with death (Table 4).

Discussion

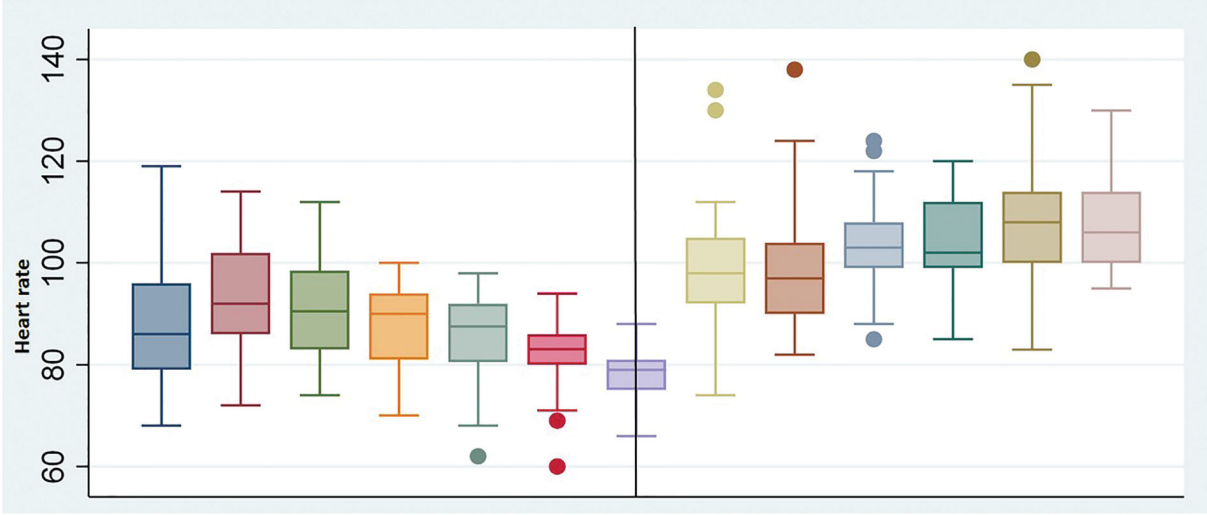
In this prospective study of 155 patients admitted to the ICU with moderate to severe OP or carbamate poisoning, high dose atropine was required in 13.6% of patients. In these patients, the addition of adrenaline infusion enabled target HR to be achieved rapidly without the need to escalate atropine dose further. Ventilation duration and ICU stay were longer in those requiring high dose atropine refractory. Although mortality was higher in the group that received high dose atropine, this was not statistically significant, probably due to the small numbers.

There are case reports [9–11] and one small case series on high dose atropine therapy in patients with OP poisoning [12]. In one report of Malathion poisoning published in 1990, the patient required 3369 mg of atropine [9]. In response to this communication, the authors [16], in a letter, highlighted other reports of high dose atropine therapy ranging from 3.9 g to over 19 g. They attributed the requirement of high dose atropine to severe poisoning and inadequate dosing of pralidoxime. In a more recent retrospective study of 25 patients with organophosphate poisoning [12], high dose atropine therapy (cumulative atropine dose ranging from 4.01 to 11.6 g) was required in three patients (12%) who also

Table 2. Hourly atropine, adrenaline and heart rate in patients requiring high dose atropine.

Hour	Atropine infusion (mean (SD) mg/h)	Cumulative atropine dose (median (IQR) mg)	Adrenaline infusion (median (IQR) μg/min)	Heart rate (mean (SD) beats/min)
−6	4.8 (2.1)	21.5 (6–50.5)	–	88 (13.1)
−5	5.5 (2.4)	27.5 (14.5–56)	–	93 (11.8)
−4	7.1 (2.8)	43 (27–63)	–	91 (10.1)
−3	10.5 (5.6)	53 (49–74)	–	88 (9.1)
−2	12.3 (9.0)	66.5 (58–83.5)	–	85 (10.3)
−1	18.1 (9.6)	93 (86–104)	–	82 (8.0)
0	21.5 (9.9)	121 (103–189)	2 (2–5)	78 (5.5)
+1	21.8 (10.6)	136 (126–220)	4 (2–8)	99 (15.4)
+2	22.7 (10.1)	166 (146–234)	4 (2–8)	100 (14.7)
+3	22.4 (9.5)	196 (166–257)	4 (2–10)	104 (10.6)
+4	21.6 (7.8)	225 (191–318)	4 (2–10)	104 (9.0)
+5	21.7 (7.7)	243 (214–343)	4 (2–6)	108 (14.1)
+6	21.9 (7.5)	262 (229–378)	2 (1–4)	108 (9.5)

Hours −6 to −1 reflect the 6 h preceding the initiation of adrenaline therapy; hour 0 reflects the time when adrenaline infusion was started; hours +1 to +6 reflect the period following initiation of adrenaline therapy; data show that the heart rate improved to >100/min following initiation of adrenaline therapy with stabilization of the dose of atropine infusion.



Hour	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6
Atropine (mg/h)	4.8 (2.1)	5.5 (2.4)	7.1 (2.8)	10.5 (5.6)	12.3 (9.0)	18.1 (9.6)	21.5 (9.9)	21.8 (10.6)	22.7 (10.1)	22.4 (9.5)	21.6 (7.8)	21.7 (7.7)	21.9 (7.5)
Adrenaline (μg/min)	-	-	-	-	-	-	2 (2-5)	4 (2-8)	4 (2-8)	4 (2-10)	4 (2-10)	4 (2-6)	2 (1-4)

Figure 1. Hourly heart rate, atropine and adrenaline requirements in patients requiring high dose atropine therapy. Hourly heart rate for six hours (marked in *x*-axis as −6 to −1) prior to initiation of adrenaline infusion and post adrenaline infusion for six hours (marked +1 to +6). The vertical line (hour 0) is when adrenaline infusion was commenced. Atropine infusion is in mg/h expressed as mean (standard deviation) and adrenaline infusion is as μg/min expressed as median (interquartile range).

Table 3. Factors associated with requirement for high dose atropine therapy.

	Bivariate analysis (OR with CI)	*p* Value	Multivariate analysis (OR with CI)	*p* Value
Age	1.03 (1.01–1.06)	.02*	1.03 (1.00–1.06)	.09
Gender	0.88 (0.30–2.59)	.82		
APACHE score	1.05 (0.99–1.12)	.12		
Lag time[a]	0.85 (0.73–0.99)	.03*	0.86 (0.74–1.00)	.04
Butyrylcholinesterase	1.00 (1.00–1.00)	.51		
IMS	2.56 (0.99–6.61)	.05*	1.41 (0.50–4.01)	.52
Type of compound[b]	1.09 (0.70–1.69)	.72		
Ventilation duration	1.06 (1.00–1.12)	.08*	1.04 (0.97–1.11)	.31
Hospital mortality	1.86 (0.47–7.33)	.37		

Ventilation predicts mortality perfectly and hence not used in the multivariate regression model, APACHE: acute physiology, age, chronic health evaluation; IMS: intermediate syndrome.

*Parameters incorporated in the multivariate logistic regression analysis if $p < .1$ on bivariate regression analysis.

[a]Lag time to presentation to hospital.

[b]Whether the compound was dimethyl, diethyl, S-alkyl organophosphorus compound or carbamate or unknown.

Table 4. Factors associated with mortality.

	Bivariate analysis (OR with CI)	*p* Value	Multivariate analysis (OR with CI)	*p* Value
Age	1.07 (1.04–1.11)	.001*	[a]	
Gender	0.77 (0.20–2.90)	.70		
APACHE II score	1.12 (1.03–1.21)	.009*	1.14 (1.04–1.25)	.004
Lag time[b]	1.04 (0.90–1.20)	.60		
Butyrylcholinesterase	0.99 (0.99–1.00)	.09		
IMS	0.53 (0.16–1.76)	.30		
DOPE	5.9 (1.53–22.45)	.01*	10.1 (2.11–48.1)	.004
Type of compound[c]	0.95 (0.54–1.66)	.86		
Ventilation duration	1.04 (0.98–1.11)	.24		
Duration of hospital stay	0.98 (0.92–1.05)	.62		

IMS: intermediate syndrome; DOPE: delayed organophosphate encephalopathy; APACHE: acute physiology, age, chronic health evaluation.
*Significant variables.
[a]Multivariate analysis was done using APACHE-II score and DOPE only since age is incorporated in the APACHE-II score; ventilation predicts mortality perfectly and hence not used in the model.
[b]Lag time to presentation to hospital.
[c] Whether the compound was dimethyl, diethyl, S-alkyl organophosphorus compound or carbamate or unknown.

received pralidoxime. The median requirement of atropine in the current study of <1 g over the first five days is much lower than the doses reported in the case reports. The use of adrenaline in our study mitigated the low HR and enabled the use of lower doses of atropine when compared to the other reports.

The current study did not demonstrate an association between the type of compound (dimethyl vs. diethyl vs. S-alkyl vs. carbamate) and the need for high dose atropine. Although a previous correspondence [16] suggested that highly lipid soluble compounds, such as fenthion, may be associated with the requirement for high doses of atropine, 21% (6/28) of patients in the current study who ingested the water soluble dimethyl compound monocrotophos [17], needed high doses of atropine. Two lipid soluble diethyl compounds, triazophos and chlorpyrifos, either on its own or in combination with pyrethroid [18], were associated with need for adrenaline infusion in three out of 12 patients (25%) and three out of 36 (8.3%) patients, respectively; there was no demonstrable difference between the combined OP-pyrethroid formulation and triazophos or chlorpyrifos. Small numbers limit further exploratory analysis.

The mechanisms contributing to a persistently low HR, the reduced HR response to atropine and the improvement in HR to adrenaline, in a subset of patients, warrant discussion. There are several possibilities: (a) high cholinesterase inhibition, induced by a high dose of inhibitors, resulting in an overflow of acetylcholine that is not adequately counteracted by the dose of atropine normally used, (b) sympathetic ganglion dysfunction, (c) desensitization of acetylcholine receptors and (d) altered adrenal catecholamine release.

It is likely that the severity of poisoning played a significant role since mega dose poisoning with concentrated OP and carbamate formulations is common in India and the blunted response to high dose atropine was due to severe cholinesterase suppression. However in our cohort of patients, the butyrylcholinesterase activity was similar in the two groups (Table 1) and there was a lack of association between admission cholinesterase activity and the requirement for high dose atropine (Table 3). However, since red cell cholinesterase more accurately reflects severity of poisoning when compared with butyrylcholinesterase, this would warrant further study. The lack of response to atropine was previously postulated to be due to inadequate dose of oximes or severe poisoning [16]. Oximes were not used in the current study and it is possible that this could have contributed to the need for high dose atropine therapy in some of our patients. Interestingly, this phenomenon has also been reported in patients treated with oximes [12].

Sympathetic ganglionic dysfunction has been reported in experimental paraoxon poisoning [19]. Administration of 0.4 or 0.8 mg/kg of paraoxon to anesthetized rabbits resulted in a slow increase in the discharge of the pre-ganglionic efferents whereas the activity of the postganglionic efferents differed. Higher doses of paraoxon blocked synaptic transmission in the paravertebral ganglia of the sympathetic trunk with a reduction in post-ganglionic activity. The resultant cardiac effects could be blocked by the timely administration of atropine [19]. Sympathetic ganglion dysfunction may thus contribute to some cardiac effects in mega-dose human OP poisoning by reducing post-ganglionic activity and release of nor-epinephrine. Exogenously administered adrenaline in this setting probably replaces the reduced natural monoamine flow and improves HR.

Persistence of acetylcholine receptor blockade can be either due to secondary blockade of receptors or receptor desensitization [20]. In animal studies, the enhanced potency of parathion-ethyl and disulfoton at elevated acetylcholine concentration was shown to be due to a persistently blocked, desensitized state [20]. In another study, Soman and echothiophate in micromolar concentrations acted as partial agonists of the n-ACh receptor and induced receptor desensitization [21]. Although this phenomenon has so far been demonstrated only in the nicotinic ACh receptors which are linked to ion channels (ionotropic receptors) where atropine would be ineffective, it is possible that similar changes may also occur in muscarinic receptors which use G-proteins as the signaling mechanism (metabotropic receptors). If such a mechanism was in play in muscarinic receptors, then a desensitized receptor state could perpetuate the low HR in OP poisoning.

Finally, it is known that the adrenal catecholamine release is under cholinergic control [22,23]. This control is however not mediated through muscarinic receptors but through nicotinic receptors [24] and hence may not be influenced by atropine. However in the clinical setting, a variable

adrenergic response to OP compounds has been demonstrated in studies. In a bovine model, methyl parathion and malathion inhibited catecholamine secretion and calcium release from adrenal chromaffin cells [25]. However in another study of diazinon treated mice, there was histological evidence of a decrease in the mean size of the adrenal medullary chromaffin cells with depletion of cytoplasmic granules which was interpreted as a hyper-catecholaminergic state; apoptosis of the chromaffin cells was also noted on histology [26]. In a cohort of 41 patients presenting with severe dichlorvos poisoning, wherein a majority of patients (90%) presented with sympathetic over-activity, catecholamine levels were elevated [27]. Thus, the effect of OP compounds on the adrenal medulla and sympathetic system may be variable and probably dependent on the type of compound, the severity of poisoning and whether the compound exhibits inhibitory or stimulatory effects on the adrenal medulla. Catecholamine levels were not measured in our study. Hence, it is unclear if our cohort of patients who required high dose atropine therapy were in a hyper or hypo catecholaminergic state prior to initiation of adrenaline therapy.

The following limitations merit mention. This was a single center study, limited by the inability to identify the compound in about 16% of patients. It is known that solvents play a role in toxicity [28] and this may have contributed to the requirement of higher doses of atropine. This was not explored in the current study. It is possible that the incidence of this phenomenon may have been overestimated by the higher threshold for target HR and the seemingly low targets for atropine infusion rate and cumulative atropine dose. The atropine thresholds in the study were set at these levels given the past experience that patients who reached these threshold often went on to require over 1000 mg of atropine, with its consequent toxicity. The higher target HR has always been set for a margin of safety in our setting given rapid and sudden reductions in HR in severe intoxication, despite being on atropine infusion. However, it is interesting to note that the proportion of patients who needed high dose of atropine in our study (13.6%) was similar to the small case series published earlier (12%). Although the above factors may limit generalizability to other settings where class I OP compounds have been banned [29] and in developed countries where patients may present very early, this study provides detailed information on a subset of patients who have a persistently low HR response in the setting of acute OP and carbamate poisoning as well as a possible therapeutic option. In this context, adrenaline may be considered as an "atropine sparing agent".

Conclusions

High dose atropine therapy was required in 13.6% of OP and carbamate poisoning at our center. It was associated with longer ventilation duration and ICU stay. Low dose adrenaline infusion helped improve hemodynamics and may limit the need to escalate atropine therapy.

Disclosure statement

There is no conflict of interest or any financial disclosures for all the authors listed in the submission.

References

[1] Peter JV, Sudarsan TI, Moran JL. Clinical features of organophosphate poisoning: a review of different classification systems and approaches. Indian J Crit Care Med. 2014;18:735–745.
[2] Peter JV, Moran JL, Graham PL. Advances in the management of organophosphate poisoning. Expert Opin Pharmacother. 2007;8:1451–1464.
[3] Eddleston M, Buckley NA, Eyer P, et al. Management of acute organophosphorus pesticide poisoning. Lancet. 2008;371(9612):597–607.
[4] Eddleston M, Buckley NA, Checketts H, et al. Speed of initial atropinisation in significant organophosphorus pesticide poisoning – a systematic comparison of recommended regimens. J Toxicol Clin Toxicol. 2004;42:865–875.
[5] Perera PM, Shahmy S, Gawarammana I, et al. Comparison of two commonly practiced atropinization regimens in acute organophosphorus and carbamate poisoning, doubling doses vs. ad hoc: a prospective observational study. Hum Exp Toxicol. 2008;27:513–518.
[6] Solti F. Malignus aritmiák [Malignant arrhythmia]. Orv Hetil. 1989;130:163–166.
[7] O'Connor PS, Mumma JV. Atropine toxicity. Am J Ophthalmol. 1985;99:613–614.
[8] Soulaidopoulos S, Sinakos E, Dimopoulou D, et al. Anticholinergic syndrome induced by toxic plants. World J Emerg Med. 2017;8:297–301.
[9] Afzaal S, Shakoor A, Rabbani MU, et al. High dose atropine in organophosphorus poisoning. Postgrad Med J. 1990;66:70–71.
[10] Hopmann G, Wanke H. Höchstdosierte Atropinbehandlung bei schwerer Alkylphosphatvergiftung [Maximum dose atropin treatment in severe organophosphate poisoning (author's transl)]. Dtsch Med Wochenschr. 1974;99:2106–2108.
[11] Golsousidis H, Kokkas V. Use of 19,590 mg of atropine during 24 days of treatment, after a case of unusually severe Parathion poisoning. Hum Toxicol. 1985;4:339–340.
[12] Karakus A, Celik MM, Karcioglu M, et al. Cases of organophosphate poisoning treated with high-dose of atropine in an intensive care unit and the novel treatment approaches. Toxicol Ind Health. 2014;30:421–425.
[13] Peter JV, Moran JL, Graham P. Oxime therapy and outcomes in human organophosphate poisoning: an evaluation using meta-analytic techniques. Crit Care Med. 2006;34:502–510.
[14] Peter JV, Prabhakar AT, Pichamuthu K. Delayed-onset encephalopathy and coma in acute organophosphate poisoning in humans. Neurotoxicology. 2008;29:335–342.
[15] Peter JV, Prabhakar AT, Pichamuthu K. In-laws, insecticide – and a mimic of brain death. Lancet. 2008;371(9612):622.
[16] Vale JA, Meredith TJ, Heath A. High dose atropine in organophosphorus poisoning. Postgrad Med J. 1990;66:878.
[17] Peter JV, Jerobin J, Nair A, et al. Clinical profile and outcome of patients hospitalized with dimethyl and diethyl organophosphate poisoning. Clin Toxicol. 2010;48:916–923.
[18] Iyyadurai R, Peter JV, Immanuel S, et al. Organophosphate–pyrethroid combination pesticides may be associated with increased toxicity in human poisoning compared to either pesticide alone. Clin Toxicol. 2014;52(5):538–541.
[19] Kullmann R, Uerdingen U. Regional pre- and postganglionic sympathetic activity during experimental paraoxon poisoning. Arch Toxicol. 1978;41:49–60.
[20] Smulders JGM, Bueters TJH, Vailati S, et al. Block of neuronal nicotinic acetylcholine receptors by organophosphate insecticides. Toxicol Sci. 2004;82:545–554.
[21] Bakry NM, el-Rashidy AH, Eldefrawi AT, et al. Direct actions of organophosphate anticholinesterases on nicotinic and

muscarinic acetylcholine receptors. J Biochem Toxicol. 1988; 3:235–259.
[22] McCorry LK. Physiology of the autonomic nervous system. Am J Pharm Educ. 2007;71:78.
[23] Thomas GD. Neural control of the circulation. Adv Physiol Educ. 2011;35:28–32.
[24] Guérineau NC. Cholinergic and peptidergic neurotransmission in the adrenal medulla: a dynamic control of stimulus–secretion coupling. IUBMB Life. 2020;72:553–567.
[25] Pei-Shan L, Luong-Sen K, Lin M-K. Organophosphates inhibit catecholamine secretion and calcium influx in bovine adrenal chromaffin cells. Toxicology. 1994;90:81–91.
[26] Raees K, Ishfaq R, Ullah A, et al. Histological and micrometric effects of diazinon exposure on adrenal medulla and cortex in mice. J Appl Anim Res. 2012;40(4):267–272.
[27] He X, Li C, Wei D, et al. Cardiac abnormalities in severe acute dichlorvos poisoning. Crit Care Med. 2011;39:1906–1912.
[28] Eddleston M, Street JM, Self I, et al. A role for solvents in the toxicity of agricultural organophosphorus pesticides. Toxicology. 2012;294:94–103.
[29] Eddleston M, Adhikari S, Egodage S, et al. Effects of a provincial ban of two toxic organophosphorus insecticides on pesticide poisoning hospital admissions. Clin Toxicol. 2012;50: 202–209.