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Atropine sulfate as a continuous intravenous infusion for the treatment of organophosphate toxicity in a cat

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Abstract

Case summary A 1-year-old male neutered domestic shorthair cat presented on an emergency basis with clinical signs suspected to be secondary to organophosphate (OP) toxicity. The control of clinical abnormalities (bradycardia, obtundation, tachypnea, anorexia) was achieved using high-dose continuous rate intravenous infusion (CRI) of atropine sulfate (maximum rate 0.1 mg/kg/h). After 5 days of hospitalization, the patient made a full clinical recovery without the development of atropine toxicity, intermediate syndrome or delayed polyneuropathy at 4 weeks after discharge.

Relevance and novel information Treatment of OP toxicity in cats is sparsely reported in veterinary literature. Current standards of treatment and published protocols recommend the use of atropine sulfate as intermittent boluses for the treatment of muscarinic signs of toxicity; however, there is a paucity of information regarding the safety and efficacy of atropine sulfate as a CRI for severe toxicosis as described in humans. This report includes the first published case using such a treatment protocol in a cat.

Keywords: Atropine; organophosphate; constant rate infusion; toxicity

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Introduction

Organophosphates (OPs) are commonly used pesticides, herbicides and insecticides that are readily commercially available in many forms for household and agricultural use. These compounds are toxic to both dogs and cats. Their adverse effects are attributed primarily to inhibition of esterases, with acetylcholine esterase (AChE) being the most clinically relevant.[1] OPs are phosphoric or thiophosphoric acid derivatives that bind to the active serine residue of AChE, rendering the enzyme inactive. This results in excessive accumulation of acetylcholine (Ach) at cholinergic synaptic terminals, causing postsynaptic muscarinic and nicotinic receptor overstimulation.[2] Clinical signs associated with OP-induced cholinergic crisis may include both muscarinic (salivation, lacrimation, urination, gastrointestinal hypermotility, diarrhea, emesis, bradycardia, bronchial secretions, dyspnea, miosis) and nicotinic (tremors, muscle twitching and spasm, paresis progressing to paralysis, respiratory failure) signs, mediated by the parasympathetic and sympathetic/somatic nervous systems, respectively. In addition, the central nervous system (CNS) contains both nicotinic and muscarinic ACh receptors, lending to potential hyperactivity, tremors, seizures, respiratory depression and bradypnea, obtundation, coma and death.[3] Clinical signs are reversible in the acute stage of intoxication; however, many OPs undergo a process termed 'aging' via hydrolysis of a phosphorous-bound

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alkyl group, resulting in permanent loss of enzymatic function.[4] Patients are at risk of the development of intermediate syndrome and delayed polyneuropathy. Intermediate syndrome manifests approximately 72–96 h after intoxication as paresis, which may progress to paralysis and respiratory failure.[5] Delayed polyneuropathy (ataxia, hypermetric gait, proprioceptive deficits) manifests 2–3 weeks after intoxication and there is no treatment.[6–9] Published treatment protocols for small animal patients include the administration of intermittent intramuscular and intravenous bolus dosing of atropine sulfate and pralidoxime (2-PAM), which act via anticholinergic and AChE enzyme re-activator pathways, respectively, to alleviate muscarinic and nicotinic clinical signs.[3,10–14] There is no established protocol describing the treatment of severe OP toxicosis in cats with continuous rate intravenous infusion (CRI) of the aforementioned medications, despite evidence that it may be beneficial in humans.

Case description

A 1-year-old male neutered domestic shorthair cat weighing 4.44 kg presented with clinical signs suspected to be secondary to OP toxicity. Approximately 18–24 h before presentation, the owner applied a flea collar containing tetrachlorvinphos (14.55%) as the primary active ingredient. The cat was found minimally responsive, anxious and dazed. The patient was an indoor/outdoor cat who was up to date on preventive vaccines and had had a flea collar placed for the first time the day before presentation. The owner reported a history of ingesting rodents and lizards on the property, but there was no known exposure to rodenticide, pesticides or other toxins.

On presentation, the patient was obtunded, tachypneic (respiratory rate 60 breaths/min) and progressively bradycardic with an initial heart rate (HR) of 180 beats per minute (bpm) that decreased to 140 bpm 1 h later. The remainder of the physical examination was unremarkable. During triage, active vomiting and defecation (soft stool) were noted.

Initial diagnostics included complete blood count, biochemistry and serum electrolytes, revealing low creatinine (0.6 mg/dl, reference interval [RI] 0.8–2.4) with the remainder of values falling within their respective established RIs. A commercially available urine drug screen test (12 Panel Quickscreen Dip Card; Pharmatech) was performed and was negative for amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, ecstasy/MDMA, methamphetamines, methadone, opiates, oxycodone, PCP and THC. Doppler systolic blood pressure was 140 mmHg. An atropine response test was performed by administering atropine sulfate 0.02 mg/kg IV, which showed no change in resting HR and static mid-range pupil size at 5, 10 and 15 mins after administration, constituting a negative response. Continuous telemetry revealed a sinus bradycardia (160 bpm). Baseline diagnostic testing was unremarkable and did not elucidate the underlying cause of the patient's clinical signs.

A presumptive diagnosis of OP toxicity was made, based on history and diagnostics. Treatment was instituted to correct the patient's clinical abnormalities. Owing to significant financial constraints, additional testing and treatments were only performed if deemed necessary by the attending clinician.

Upon admission, an intravenous catheter was placed. Intravenous fluid therapy was provided with lactated Ringer's solution (LRS; Vetivex Lactated Ringer's Injection USP; Dechra Veterinary Products) at a rate of 3.75 ml/kg/h. Additional treatments included maropitant (Cerenia 10 mg/ml; Zoetis) 1 mg/kg IV every 24 h, atropine sulfate (Atropine sulfate 0.54 mg/ml; VetOne) 0.05 mg/kg IV once, atropine sulfate 0.15 mg/kg IM once and lipid emulsion (Intralipid Caloric Agent Fat Emulsion 20%; Baxter) 1.5 ml/kg IV bolus for 5 mins followed by 0.25 ml/kg/min over 60 mins. The patient was bathed with dish detergent for the purpose of topical decontamination.

After administration of the aforementioned atropine doses, no further inappropriate defecation or vomiting were noted; however, bradycardia and obtundation were recurrent throughout hospitalization. The cat's respiratory rate improved to 32 breaths/min, HR increased to 180–190 bpm and mentation became normal. During the first night of hospitalization, the patient was prescribed atropine (0.026 mg/kg IV q4h as needed) for the correction of recurrent muscarinic clinical signs consistent with OP toxicity. However, bolus dosing was necessary every 1–2 h in order to control recurrence of signs. Blood pressure and physical examination indicators of tissue perfusion (mucous membrane color, capillary refill time and pulse quality) remained normal. Upon re-evaluation of the patient 12 h after hospitalization, the rate of intravenous fluid therapy was decreased to 2.5 ml/kg/h and a CRI of atropine was initiated (0.005–0.02 mg/kg/h IV). The initial rate was extrapolated from the patient's hourly dosing, while carefully monitoring for signs of atropine toxicity. A minor positive response was initially noted, but dose escalation was necessary to control persistent bradycardia, obtundation and anorexia.

An additional intravenous atropine bolus (0.025 mg/kg) was administered before increasing the atropine CRI to 0.04 mg/kg/h. Over the course of the first 24 h in hospital, the atropine CRI was titrated to a rate of 0.1 mg/kg/h. At this increased rate, the patient's HR remained between 160–190 bpm and clinical improvement was noted.

On day 2 of hospitalization, weaning of the infusion was attempted, but unsuccessful. A decrease in the rate

to 0.02 mg/kg/h for 4 h, followed by temporary discontinuation, resulted in recurrent bradycardia (120–130 bpm), obtundation, lethargy and anorexia. An intravenous bolus of atropine (0.05 mg/kg) was administered, and the CRI was restarted at 0.04 mg/kg/h. The patient's HR was subsequently noted to increase to 170–180 bpm, with improved mentation and return of normal appetite. Venous blood gas analysis revealed pH 7.425 (RI 7.335–7.446), pCO_2 40.6 mmHg (RI 35–46 mmHg), HCO_3^- 25.1 mmol/l (RI 18–27) and lactate 0.6 mmol/l (RI 0.4–1.5).

On day 3 of hospitalization, the patient failed a second weaning trial with discontinuation of the atropine CRI resulting in obtundation and bradycardia (HR 120–130 bpm). Again, an additional intravenous bolus of atropine (0.08 mg/kg) was administered, followed by re-initiation of the CRI at 0.1 mg/kg/h for 12 h. The atropine CRI was weaned with a rate of 0.05 mg/kg/h for 4 h and a rate of 0.02 mg/kg/h for 2 h before discontinuation. At this time, the patient remained clinically stable and did not experience a change in clinical status. He was discharged after 4 days of hospitalization and was noted to be clinically normal in his home environment 48 h, 1 week and 4 weeks after discharge from the hospital.

Discussion

Atropine CRIs have been successfully used in people presenting for OP toxicity, with reports of decrease in time to atropinization and reduction in morbidity and mortality. Recommended strategies include the implementation of rapid incremental dosing of atropine IV (bolus dosing range 1–10 mg) every 5–30 mins, followed by a CRI (starting rate 0.02–0.08 mg/kg/h) titrated to effect for an estimated 24–72 h to control clinical signs;[15–19] however, it is important to note that there is no concrete consensus on dosing regimens.[20] Several reports include the use of adjunctive therapies that were not included in this case, such as concurrent hemoperfusion and infusion of pralidoxime; however, rapid atropinization and continuous infusion is shown to have a positive independent effect on morbidity and mortality.[16–19] Pralidoxime was not available at the time of admission, procuring the medication would have been cost-prohibitive and the patient was not clinical for the nicotinic signs associated with OP toxicity.

In the present case, intermittent bolus dosing was not sufficient to control the clinical signs associated with OP toxicity. As previously noted, the initial rate of the CRI was calculated based on the patient's previously prescribed hourly dosing regimen; however, it is also in accordance with the published guidelines utilized in the treatment of humans.[15–19] It should be noted that HR was not targeted as an indicator of necessity for therapy given the patient's cardiovascular stability throughout treatment, but rather was a measurable parameter that coincided with the patient's change in clinical status during the course of hospitalization. Rapid incremental dosing was not performed before CRI due to the risk of atropine toxicity and the perceived safety of slow titration despite evidence that this may be a superior method of administration in humans. Weaning and discontinuation of atropine were based solely on the patient's clinical status and lack of refractory signs of toxicity. There is evidence of serum lactate as a marker for successful weaning in humans, but serial lactate measurements were not obtained due to financial constraints.[21] The patient's resolution of clinical signs and lack of continued dependence on atropine after treatment with a CRI was similar to what is reported in the human literature. Unfortunately, confirmatory testing for esterase levels was not possible, due to financial constraints. Follow-up after discharge confirmed that the patient did not suffer from clinical signs consistent with intermediate syndrome or delayed polyneuropathy, both of which have been documented in humans, dogs and cats.[5–9] This may be due to the biochemical profile of tetrachlorvinphos in cats; however, there are no published data on its duration of action, propensity for aging, metabolism or excretion in this species. Furthermore, the lack of delayed signs is likely unrelated to the treatment protocol used in this case, as atropine is not shown to prevent these disease processes from occurring.

Conclusions

In this case, a presumptive diagnosis of OP toxicity in a cat was made based on history and timeline of exposure, clinical signs, lack of test results consistent with an alternative diagnosis and response to empiric therapy. Reports in people suggested that the use of atropine sulfate via CRI may be beneficial in the treatment of severe OP toxicity. The present case documents the use of an atropine sulfate CRI, which was shown to be safe, effective at ameliorating clinical signs, readily titratable and logistically feasible in the treatment of OP toxicity in a cat. Further investigation is warranted regarding the use of atropine infusions in cats.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognized high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open*

Reports. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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