COMPANION OR PET ANIMALS

Pyridostigmine bromide intoxication in two domestic cats

Koen Maurits Santifort,[1] Matthijs van Luin,[2] Paul Mandigers[3]

[1]Neurology department, Veterinair Verwijscentrum de Pietersberg, Oosterbeek, The Netherlands
[2]Apotheek, Ziekenhuis Rijnstate, Arnhem, The Netherlands
[3]Department of Clinical Sciences of Companion Animals, Universiteit Utrecht Faculteit Diergeneeskunde, Utrecht, The Netherlands

Correspondence to
Koen Maurits Santifort;
koensantifort@gmail.com

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SUMMARY

A one-year-old female neutered cat died soon after presentation with severe signs of a cholinergic crisis. Its sibling was presented soon thereafter, in which cholinergic signs were also readily apparent. The owner, a myasthenia gravis patient, used pyridostigmine bromide tablets, and it was hypothesised that a pyridostigmine bromide intoxication was the cause of this cholinergic crisis. Treatment with 0.1 mg/kg atropine injected intramuscularly soon alleviated most of the cholinergic signs. Additional treatment, which included decontamination with enteral activated charcoal, intravenous fluid therapy, laxation and supportive care, as well as repeat administration of atropine, resulted in resolution of signs after 48 hours. A serum sample collected 30 hours after admission revealed that the total cholinesterase activity was reduced by 44 per cent, compared with a baseline value measured in a sample taken three weeks after the intoxication. This is the first report of human-prescribed pyridostigmine bromide intoxication in domestic cats.

BACKGROUND

Exposure to drugs intended for human use is one of the main causes of intoxication in small animals, accounting for about 30 per cent of all intoxications.[1–3] Accidental ingestion of improperly stored drugs is mostly seen in dogs compared with cats and other species.[1] Drugs with an effect on the CNS and NSAIDs are frequently involved, although many other classes of drugs have been reported causes of toxicosis in pets. The most frequent causes of intoxication in pets are the systemic administration or topical application of insecticides such as organophosphates (OP) or carbamates (CB).[4] These substances inhibit acetylcholinesterase (AChE) irreversibly (OP) or reversibly (CB) and produce muscarinic, nicotinic and CNS signs often referred to as a cholinergic crisis.[4–7] This case report describes the clinical signs, diagnosis, treatment and end results of intoxication with pyridostigmine bromide, intended for human use, in two domestic cats.

CASE PRESENTATION

- Species: feline (two siblings).
- Breed: domestic shorthair.
- Sex: female, neutered.
- Date of birth: one year old at presentation.
- Weight at presentation: 3.5 and 3.0 kg.

A one-year-old, 3.5 kg, female neutered cat was presented for evaluation after the owner found the cat in a semicomatose state. The cat, its sibling and a dog were alone in the house with food and water. The cats were kept indoors, and according to the owner no recent drugs or antiparasitic treatment had been administered/performed during the last few weeks.

On presentation, the cat was in lateral recumbency and seemingly comatose. The airway was deemed patent, the tongue was cyanotic, breathing was extremely shallow and a bradycardia (60/minute) with weak femoral pulse was noted. Other clinical findings were generalised muscle hypertonicity, myokymia and fasciculations, enophthalmus, miosis, protrusion of the nictitating membrane, profuse salivation, absent corneal reflexes, and severely depressed spinal reflexes with a tonic response to the withdrawal reflex test with claws protracted. Also, a faint vocalisation was noticed when moving the cat. When preparations for stabilisation were contemplated during the exam, anisocoria was noticed with subsequent bilateral mydriasis and a decerebrate posturing (possibly a tonic seizure). Femoral pulse was absent and cardiac auscultation revealed no sounds. Resuscitation failed. The owner consented to postmortem examination, which revealed no gross abnormalities, but in the stomach a granular, yellowish substance was found.

Thirty minutes later, the owner arrived with her other cat (one-year-old, 3 kg, female neutered (sibling)). This cat showed similar, although less severe, signs as the just deceased sibling: generalised paresis, fasciculations on attempt at movement, bradycardia (100/minute), enophthalmus, miosis, protrusion of the nictitating membrane, as well as decreased mentation (sopor), decreased palpebral reflex, weak spinal reflexes, lacrimation, salivation and spontaneous gagging. Breathing was slightly shallow, but costoabdominal with a frequency of 36 breaths/minute. During the examination, the owner was again asked about possibilities of intoxication or recent drug administrations, which were denied again. On asking if the owner had any medication stored in the living spaces of the cats, it was noted that she had both pyridostigmine bromide (60 mg tablets) and atropine (600 µg tablets) tablets (for myasthenia gravis (MG) of the owner). At this point, since both cats showed signs of a cholinergic crisis, intoxication with pyridostigmine bromide was suspected.

INVESTIGATIONS

A serum sample, taken 30 hours after admission, was analysed for total cholinesterase (ChE) activity

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and bromide levels, which were 1900 U/l and 1769 mg/l, respectively. A serum sample taken at the three-week check-up showed ChE activity and bromide levels of 3400 U/l and 12.1 mg/l, respectively. Based on the second (baseline) AChE activity level, the first sample showed a 44 per cent decline in AChE activity.

The tests were performed at Euregio Laboratory Services BV, Stadionplein 46, 6225 XW Maastricht, The Netherlands. A spectrophotometric assay as described by Tecles and Cerón[8] was used to determine ChE activity levels.

DIFFERENTIAL DIAGNOSIS

Considering the fact that two cats in the same household were presented with similar signs of different severity, differential categories considered in these cases were toxic (OP, CB or human prescription drugs) and nutritional. Infectious and inflammatory aetiologies were deemed unlikely.

TREATMENT

Atropine was injected intramuscularly at a dosage of 0.1 mg/kg. Five minutes later, the cat lifted its head and, with help, was able to maintain a sitting position, although fasciculations were still noticeable. Bilateral mydriasis was evident. Salivation was subjectively decreased and no gagging was noticed. Heart rate increased to 200 beats/minute. During the next 36 hours, intravenous fluid therapy was instigated and maintained, and activated charcoal, a laxative and a high-energy fluid diet were administered via a naso-oesophageal tube, and atropine intramuscularly (0.1 mg/kg) was repeated two times at four and nine hours after first administration. At each of these time moments, miosis, salivation and gagging indicated cholinergic overstimulation, which receded a few minutes after intramuscular administration of atropine.

OUTCOME AND FOLLOW-UP

Eighty-four hours after intake, the cat was bright, alert and responsive, able to move around normally, and no cholinergic signs were noted. One week later, the owner reported no further abnormalities. A check-up three weeks later revealed no abnormalities in general and neurological examinations and no recurrence of cholinergic signs was noted. The owner has taken precautions to prevent future ingestion of prescription drugs by the cat.

DISCUSSION

Pyridostigmine bromide is the bromide salt form of pyridostigmine. Pyridostigmine is a quaternary ammonium CB derivative and (acetyl)cholinesterase inhibitor with a relatively long duration of action (about three to four hours) and onset time is generally within one hour[5 9 10] (National Center for Biotechnology Information 2017–1[11]). Renal elimination is about 75–90 per cent. By reversibly binding to AChE, it prevents breakdown of acetylcholine at cholinergic synapses, facilitating neuromuscular transmission. Muscarinic and nicotinic receptors mediate the effect of acetylcholine in the peripheral nervous system (parasympathetic and somatic) and CNS (pyridostigmine possibly mediates CNS effects via other mechanisms as well).[4 12–16] At synapses in the autonomic ganglia, nicotinic receptors mediate cholinergic neurotransmission.[14–16] Pyridostigmine bromide is commonly used by veterinary patients for treatment of MG.[7 17 18] The usual dosage in cats is lower than in dogs (0.5–3 mg/kg divided twice a day/three times a day) and the side effects are more often reported in this species.[4 7 9]

The side effects and signs of overdose and intoxication with pyridostigmine bromide resemble those typically encountered in cases of intoxication with other (often irreversible) AChE inhibitors, such as OP and CB.[7 15 16 19] Pesticide exposure is a common cause of intoxication in human as well as veterinary cases.[4 16 20 21] Pyridostigmine bromide poisoning in domestic cats has not been reported in the literature. In the period of 2006–2016, the National Poisoning Information Center (NVIC) of the University Medical Center of Utrecht, The Netherlands, has been consulted eight times for exposure of dogs to pyridostigmine.[22] Intoxication with AChE inhibitors leads to a spectrum of cholinergic signs mediated through muscarinic receptors denoted with the term 'SLUD' or 'SLUDDE'.[4 5 7 16 19] SLUDDE stands for salivation, lacrimation, urination, defecation, dyspnoea and emesis.[4 5] Bradycardia and miosis are also mediated through muscarinic receptors, although it might also be a direct effect of some AChE inhibitors.[4 5 14] SLUDDE signs are the result of stimulation of glands and smooth muscle and together constitute what is known as a 'cholinergic crisis'.[4 5 7 19] Nicotinic signs due to interference with skeletal neuromuscular neurotransmission are also seen and are partly excitatory (eg, fasciculations) and partly inhibitory (paradoxical paresis and respiratory paralysis).[4 5] Nicotinic signs may predominate over muscarinic signs; respiratory paralysis may be present without SLUDDE signs.[5 7] Paralysis is often reported to be flaccid, suspected to be due to excess nicotinic stimulation at the neuromuscular junctions of the skeletal muscle, although the most severely affected cat in this case did not display flaccid paralysis but rather generalised paresis with tetanus-like muscle action on stimulation. CNS actions of pyridostigmine bromide have been suggested, although it does not readily cross the blood–brain barrier.[14 23] CNS signs of hyperactivity, ataxia, seizures and coma are also described and were present in the fatal case reported here.[4] Respiratory failure or cardiac arrest may result from an interplay of all these effects, which is often the cause of death in cases with a fatal outcome.[4 19] In human beings, signs that cannot be objectively evaluated in veterinary patients such as blurry vision and abdominal cramps are reported after overdose of pyridostigmine and exposure to AChE inhibitors (pesticides and chemical warfare agents).[5 15 16]

Signs of intoxication with pyridostigmine bromide, specifically, might also be related to the bromide ions released in the blood after uptake of the compound, as has been reported in a human case (eg, psychoses[24]). Adverse effects of treatment of feline epilepsy with potassium bromide have been reported extensively (mainly affecting the airways, ie, airway hypersensitivity, but also pancreatitis and gastrointestinal signs), and bromide is therefore not a recommended antiepileptic drug in this species.[25] Such side effects are not likely to occur acutely and would be expected to occur after repeated doses have been ingested (especially airway hypersensitivity). No delayed side effects were reported in the surviving cat in this case.

Severity and duration of clinical signs of AChE inhibitor intoxication depend on the compound, dose, treatment (appropriate and timely) and signalment. Regarding the latter, species (cats are considered more susceptible than dogs) and age (very young and very old at higher risk) in addition to concurrent illness are factors reported to be of influence.[4 7] These factors also influence prognosis, which is good if treatment is initiated early on and no signs of respiratory distress or CNS involvement are present.[4]

AChE inhibitor intoxication is a clinical diagnosis, which means that if typical clinical signs are noted in a patient with

suggestive anamnestic clues, treatment should be instigated forthwith.[16 19] Diagnostic tests of value are mainly focused on identification of the toxicant or its effect, that is, AChE inhibition. As in any intoxication, direct identification of (abnormally high levels of) the toxicant in a patient sample (eg, blood or urine) would be considered the gold standard. In this case, direct toxicant identification tests were not available in the contacted human laboratory.

All tests are always to be correlated to the clinical signs of the patient. One diagnostic test is the determination of ChE activity in the whole blood, plasma or serum. It is imperative to understand the physiology of ChE enzymes in normal individuals for correct interpretation of these tests. Basically, two forms of ChE enzymes are present in mammals: AChE and pseudocholinesterase (PsChE, also called serum/plasma cholinesterase or butyrylcholinesterase).[8 16 20 26 27] AChE is present in the tissue, red blood cells and synapses, whereas PsChE is found in different tissues and serum. Several variants of PsChE exist.[8 26 27] These enzymes differ in their substrate specificity, with PsChE being less specific than AChE.[8 16 26 27] Also, PsChE is more sensitive to inhibition. Both enzyme activities can be measured in several ways, which are described in the literature, although efficient and accurate dissection of AChE and PsChE activity is not regarded to be feasible.[8 16 26 27] The total ChE activity is determined by the activities of both enzymes in different ways in different species. In cats, dogs and human beings, activity levels vary but approximate a more equal distribution in the whole blood.[8 20 26 27] Although the function of PsChE is largely unknown, total ChE activity testing in serum is useful for the diagnosis of poisoning with (acetyl)ChE inhibitors.[8 16 26 27] Testing of ChE activity is neither a sensitive nor specific test, and there is a wide variation in 'normal' values between individuals and fluctuations in test results in individuals are common.[8 16 26 27] Therefore, baseline testing to determine pre-exposure activity levels in people who have an occupational risk for exposure to AChE inhibitors is often mandatory and a logical prerequisite for useful interpretation of tests (in all mammals) when toxicity or exposure is suspected.[8 16 20 26 27] Test results can be expressed as a percentage of baseline values, always using the same sample type and method.[16] Usually, a greater than 50 per cent decrease is suggestive of exposure to an AChE inhibitor, with a greater than 75 per cent reduction leading to severe signs of toxicity.[6 8 16 20 26 27] The use of these tests in several animal species including cats has been studied and in some texts doubts are shed on its usefulness, the usual argument being that PsChE activity in cats is significant. Still, in the authors' opinion, due to factors such as interspecies similarities and use of individual reference values, there is no reason to suspect the same interpretation methods used in human beings might not be applicable to felines.[6 8 26 27]

In this case, we tested the total ChE activity and bromide levels in serum on two occasions (30 hours after admission and three weeks later). A 44 per cent reduction (compared with baseline) in ChE activity in a sample obtained 30 hours after admission was deemed to be very suggestive of exposure to AChE inhibitors. The elevated serum bromide level confirmed the ingestion of pyridostigmine bromide as the bromide level (1769 mg/l) found is much higher than expected in a normal cat.[25] After three weeks, the bromide level was significantly lower (12.1 mg/l), as would be expected based on reported clearance of bromide.[25] These results corroborate the diagnosis of pyridostigmine bromide intoxication and provide a high degree of certainty.

The three week check-up served three main purposes: (1) to check if no delayed neuropathy signs were present as has been reported in the literature with other AChE inhibitors (OP), (2) to check if no residual adverse effects of any kind were readily apparent, and (3) to collect another serum sample to establish baseline AChE levels (and repeat bromide level assessment).[16 25 28]

As mentioned earlier, intoxication with AChE inhibitors is a clinical diagnosis, so test results should never be interpreted in isolation.[4 16 19] Clinical signs, fitting test results and response to treatment form the basis of a correct diagnosis. If cholinergic signs are clear and intoxication was witnessed or the drug was in the habitat of the animal, the diagnosis may be assumed with near certainty and appropriate treatment should not be delayed as this may prevent a fatal outcome.

Regarding treatment, anticholinergic drugs (also classified as parasympathicolytics) such as atropine or glycopyrrolate are indicated when toxicosis due to AChE inhibitors is diagnosed.[7 14] Glycopyrrolate, however, has been reported to be less effective in countering the muscarinic effects of AChE inhibitors, although blockade of nicotinic receptor sites may be beneficial.[9 14] Atropine is the antimuscarinic drug of choice (except in rabbits).[5 7 9] Both these drugs are associated with quite severe adverse effects and overdosage in turn may be associated with severe and life-threatening consequences (eg, cardiovascular collapse).[9 16] If there is doubt as to whether or not AChE inhibitors are the cause of the signs in a patient, a low, preanaesthetic dose of atropine (0.02–0.04 mg/kg intravenously) is recommended.[7] Usually, it takes higher doses to negate the effects of OP/CB poisoning, although this is obviously subjected to many variables such as those of influence on the signs that can be present as mentioned earlier. If presenting signs persist in combination with a swift onset of mydriasis and tachycardia, AChE intoxication might be considered unlikely.[4 7] However, regarding dosage of atropine, accurate or definite recommendations on dosages in emergency settings cannot be made due to several complicating and case-dependent factors. The dose of toxicant is often unknown, cointoxication is always a possibility and clinical signs may have just manifested or may have been progressing for a while. A wide range of 0.02 mg/kg up to 2 mg/kg (extreme) can be distilled from several texts, but if suspicion is high and signs are moderate-severe, a dose of 0.1–0.25 mg/kg intramuscularly or intravenously repeated as needed might be a reasonable compromise.[4 6 9] In this case, intramuscular administration of atropine in a dosage of 0.1 mg/kg was chosen due to moderately severe signs in the second presented cat.

Emergency treatment of cats (or dogs) with suspected or confirmed intoxication with an AChE inhibitor is not limited to administration of anticholinergic drugs. Immediate life-saving actions are necessary when animals are presented with severe cardiovascular or respiratory signs as cardiac arrest and respiratory failure are the most common causes of death in intoxication with an AChE inhibitor, as unfortunately illustrated by the first cat that was presented in this case.[5 7] Intubation and mechanical ventilation, in addition to pharmacological treatment, are necessary in these cases.[5 7] Obviously, in such cases, it is always particularly difficult to decide when there is enough certainty to administer specific drugs (such as atropine) to counter suspected toxic effects. The clinician can only do his/her best to decide if the benefits outweigh the risks (discussed above) in each case.

In conclusion, this is the first reported case of intoxication due to accidental ingestion of an AChE inhibitor (pyridostigmine bromide) intended for human use in domestic cats. The possibility of a fatal outcome is clear, as was the case in one of the cats that showed more severe signs, probably due to ingestion of a higher dose or earlier ingestion than the other

cat. The importance of a thorough and comprehensive anamnesis in emergency patients with signs possibly due to intoxication cannot be overstated. For example, as in this case, owners might not realise that their own medications (which they believe to be stored safely) may be the cause of intoxication. Adequate treatment, including administration of atropine via intravenous or intramuscular routes, is vital to achieving good outcomes in intoxication with pyridostigmine bromide.

OWNER'S PERSPECTIVE

The owner reported that she had never considered the possibility that her cats might eat tablets of hers. She keeps the medication stored in places the cats cannot reach from this point on.

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