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TITLE

Alpha-chloralose poisoning in a cat

SUMMARY

A five-year-old domestic cat with acute unexplainable neurologic symptoms was presented for necropsy. Clinically, the cat showed an acute onset of ataxia, depressed mentation and continuous twitching/seizure activity in the morning after having been outside overnight. Despite immediate treatment, the cat progressed within twenty-four hours to a comatose state, opisthotonus and severe miosis unresponsive to light. Given a poor prognosis, euthanasia was elected. Gross findings were disappointing and consisted of a non-specific lung oedema and congested lungs and spleen. Surprisingly, within the stomach and intestines, fragments of cockshafers were found. Histologic examination confirmed the gross findings and additionally showed evidence of mild brain oedema, but failed to identify a cause for the severe clinical symptoms. In a final attempt to solve the case, a urine sample was tested for toxic substances and it was found to contain a significant amount of alpha-chloralose. This finding was unexpected.

BACKGROUND

The cause of disease was unexpected in this case. Alpha-chloralose (AC) is used within and outside the UK to kill or immobilize pest animals. Cases of accidental AC poisoning in people are reported, whereas AC intoxication is only poorly described in pet animals.

To the authors' knowledge, this report describes the first case of chloralose intoxication in a cat within the UK. Chloralose poisoning should be considered as differential diagnosis in cases with unexplainable neurological symptoms in animals and men.

CASE PRESENTATION

A five-year and ten-months-old ginger domestic cat presented with an acute onset of ataxia and disorientation progressing to depressed mentation and continuous twitching/seizure activity in the morning after having been outside overnight. The cat was immediately treated with a dose of 0.5 mg/kg diazepam and 300 mg/kg bolus of lipid infusion for suspected intoxication by the referring veterinary surgeon. Full blood examination was unremarkable. Referral was initiated as the clinical signs progressed to recumbency and severely reduced mentation with continuous twitching/seizure activity. The cat presented in lateral recumbency, was salivating, showed chewing movements and was hyperaesthetic. Physical examination showed hypothermia (37.1 °C), which continued throughout hospitalization. Neurological examination showed a severely obtunded cat with continuous tremors particularly affecting the fore limbs and the face suggestive of seizures activity. Cranial nerve examination showed symmetrical miotic pupils responsive to light and an impaired oculovestibular response. Postural reactions were absent. Based on the neurological examination, the lesion was localized to forebrain and brainstem. Increased intracranial pressure was suspected. Immediate treatment with 4 mg/kg intravenous phenobarbitone led to discontinuation of the seizures. Thereafter, the cat became stuporose. Overnight treatment included multiple dosages of 0.5 g/kg intravenous mannitol, intravenous fluid therapy, regular turning, and urinary bladder management. Monitoring included echocardiography, blood pressure assessment, and clinical assessment of mentation, pupil size and pupillary light response. Clinical signs of waxing and waning persisted, with episodes of slight improved mentation, marked hypersensitivity to noise, followed by severe miosis, comatose appearance and opisthotonus. The cat owner elected euthanasia the following morning due to the lack of improvement and the overall poor prognosis. A full post-mortem examination was requested.

INVESTIGATIONS

Gross pathology:

On gross examination, the findings were disappointing and limited to unspecific lesions in the lungs and spleen. The lungs appeared moderately oedematous and congested, while the spleen was markedly congested (Figure 1). These findings were interpreted as likely associated with euthanasia. Upon examination of the gastrointestinal contents, the stomach contained a partially digested furball and,

surprisingly, fragments of insects that were identified as rose cockshafers, also known as May bugs (Figure 2). Small intestinal contents appeared unremarkable, while the colon contained fragments of cockshafers and a moderate amount of dark green, soft, fluid-rich ingesta (Figure 3). No other gross abnormalities were detected.

Histopathology:

Tissue samples from various organs and brain were fixed in 10 % formalin and routinely processed and stained with haematoxylin and eosin for histologic examination. Histology confirmed the gross findings of lung oedema and congestion of lung and spleen. In addition, mild perivascular oedema in the brain was observed in the thalamus and both cerebral hemispheres. No other relevant histologic findings were observed.

Toxicology:

Due to the non-specific pathologic findings and the clinical suspicion of intoxication, a urine sample was tested for toxic substances. Tested by gas chromatography - mass spectrometry (GC-MS), the urine sample was found to contain a significant amount of alpha-chloralose (AC), which led to the final diagnosis of AC poisoning in this case. The sample was analysed by qualitative GC-MS and went through a full 50-600 mass-to-charge ratio (m/z) scan with library matching. The library matching process detected AC with a 91 per cent match and did not detect the beta analogue at all. The GC-MS assay is qualitative, with typical limits of detection of approximately 1 ppm or less. The peak total area was up to three times that of an included diphenylamine 2 ppm internal standard.

DIFFERENTIAL DIAGNOSIS

The list of differential diagnoses for acute central neurological symptoms in cats is vast. Degenerative, anomalous, metabolic, nutritional, neoplastic, inflammatory (infectious and non-infectious), idiopathic, iatrogen, toxic, traumatic and vascular lesions all have to be considered. In a five-year-old cat, congenital anomalies and tumour may be less likely, but cannot be ruled out. Toxic causes of neurological signs in cats include heavy metals (e.g. lead, mercury), certain mushrooms (e.g. *Amanita* species pluralis, *Gyromitra* species pluarlis, *Helvella* species pluarlis) and mycotoxins (e.g. fumonisin B1), neurotoxic plants, insecticides (e.g. organophosphates, carbamates), pesticides (e.g. aminopyridine, bromethalin, chlorinated hydrocarbons, metaldehyde, strychnine, zinc phosphide), antifreeze (e.g. ethylene glycol), methylxanthines (e.g. caffeine, theobromine, theophylline) and certain drugs of abuse (e.g. amphetamines, marijuana, nicotine) (Haschek and others 2013, Peterson and Talcott 2013). The vast majority of the mentioned non-toxic lesions show characteristic changes on histopathologic examination of the brain. In most cases of toxicity, including AC poisoning, histological changes are, however, often absent or non-specific and toxicological testing is required to reach a diagnosis.

TREATMENT

When first presented to the referring veterinary surgeon, the cat was immediately treated with a dose of 0.5 mg/kg diazepam (Diazepam injection BP. Hameln Pharmaceuticals GmbH, 31789 Hameln, Germany) and 300 mg/kg bolus of lipid infusion (Intralipid 20%, Fresenius Kabi Limited, Cheshire, WA7 1NT, UK) for suspected intoxication. Due to clinical worsening, the cat was then brought to a referral hospital where the veterinarian suspected increased intracranial pressure and immediately treated the cat with 4 mg/kg intravenous phenobarbitone (Phenobarbital Sodium Injection. Martindale Pharmaceuticals, Bampton Road, Harold Hill, Romford, RM3 8UG, UK). Overnight treatment included multiple dosages of 0.5 g/kg intravenous mannitol (Mannitol 10% w/v. Fresenius Kabi Limited, Cheshire, WA7 1NT, UK) and intravenous fluid therapy. Due to the stuporous and later comatose state, the cat was regularly turned and the urinary bladder was regularly assessed and manually emptied every four hours. Due to the lack of improvement, the severe neurological symptoms and financial restraints, the cat owner elected euthanasia the following morning.

OUTCOME AND FOLLOW-UP

Despite treatment, clinical signs of waxing and waning persisted, with episodes of slight improved mentation, marked hypersensitivity to noise, followed by severe miosis, comatose appearance and opisthotonus. The cat owner elected euthanasia and requested a full post-mortem examination. After a thorough gross and histologic examination of the entire body, the cause of disease could not be identified. As intoxication seemed likely, a urine sample was screened for toxic substances and was found to contain a significant amount of alpha-chloralose (AC). The way of AC intake in this case remains unknown, but is suspected to have occurred by ingestion. At necropsy, there was no evidence of ingested bird or rodent material. The presence of cockshafers in the stomach and large intestine was however surprising and is highly suspected to be associated with the poisoning in this case. The authors suspect that the cat may have been poisoned by ingestion of cockshafers previously poisoned with AC. The owner of the cat was informed about the final diagnosis and the health risk of AC for animals and people.

DISCUSSION

Alpha-chloralose (AC), a chlorinated acetal derivative of glucose, is used as a rodenticide, avicide and repellent, often in form of hypnotic baits to immobilize and live-capture pest animals (O'Hare and others 2007). It is moderately toxic to mammals and fish, and highly toxic to birds (Cornwell 1969, Hertfordshire University 2015, Loibl and others 1988, Thomas and others 1988). The mode of action of AC is not fully understood. So far, it is known that chloralose is first metabolized to chloraldehyde or chloral, which is mainly transformed into trichloroethanol (a metabolite of chloral hydrate) (Riviere and Papich 2009, Lees and others 1972). Trichloroethanol is an active metabolite, which is assumed to interact with the gamma-aminobutyric acid (GABA) receptor, leading to depression of the cortical centers of the brain. Due to the formation of trichloroethanol, the effects of AC are similar to those of chloral hydrate i.e. sedation, respiratory depression and hypotension. While AC causes a depression of the central nervous system (CNS), baroreceptor reflexes, vasomotor centres, or spinal reflexes are not depressed. Spinal reflex activity may however increase to the degree that muscle activity ("convulsions") develops (Riviere and Papich 2009). There is little indication that AC has an analgetic effect (Riviere and Papich 2009). In humans, AC is known to be harmful by inhalation and if swallowed, narcotic and irritating to eye, skin and respiratory tract (Hertfordshire University 2015). It is classified as moderately hazardous by the World Health Organization (WHO) classification. Within the United Kingdom (UK), the use of AC is restricted, and members of the public who want to possess or use it must hold an explosives precursors and poisons (EPP) licence issued by the Home Office (Government UK 2016).

In people, both accidental and intentional AC poisoning with either fatal or non-fatal outcome has been reported (Federici and others 2006, Gerace and others 2012, Thomas and others 1988). Typical clinical features included coma and generalized convulsions (Thomas and others 1988). In animals, accidental AC poisoning is only poorly reported. To the authors' knowledge, there is only one scientific peer-reviewed study from Israel about AC intoxication in pet animals (Segev and others 2006). In this retrospective study, Segev et al. (Segev and others 2006) describe 33 canine and 13 feline cases with detailed clinical findings, but only limited information about post-mortem changes. The most common clinical signs were seizures, muscle tremor, hyperaesthesia, hypothermia, salivation, miosis, stupor,

coma and ataxia. Coma and hypothermia was more common in cats, whereas salivation, ataxia and hyperthermia was more frequently seen in dogs (Segev and others 2006). Out of the total 46 cases, one dog and two cats died. A post-mortem examination was performed of the two cats, which revealed no abnormal findings. The prognosis of AC poisoning is primarily species and dosage-dependent and can lead to death in severe cases (Segev and others 2006). Without much doubt, the time-lag from exposure to admission is highly relevant for the prognosis. In outdoor cats, the time of exposure is however often undetermined, and outdoor cats are more likely to be presented later in the course of the disease. In the study of Segev et al. (Segev and others 2006), two out of 13 cats and one out of 33 dogs died respectively, leading to a rather low overall mortality of 6.5%. The two cats died one and five hours post admission, respectively. Both cats were presented in a state of coma like the case herein reported. One of the cats was presented 24 hours post exposure, and died of acute renal failure, most likely due to dehydration. In conclusion, the overall prognosis, with supportive, symptomatic and anticonvulsant therapy appears to be good. Scientific reports about AC poisoning and its prognosis in cats are however rare. AC poisoning in pet animals within Europe or the United States is poorly reported and no case has been described within the UK, as far as the authors are aware.

LEARNING POINTS/TAKE HOME MESSAGES

- Alpha-chloralose (AC) is a substance that is used to immobilize or kill pest animals within and outside the UK
- Depending on the dosage, AC can be toxic for animals and people and causes neurologic clinical symptoms
- Gross and histopathologic findings are non-specific in cases of AC poisoning
- Toxicological testing is needed to diagnose AC intoxication

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FIGURES



Figure 1. Photograph of the severely and diffusely congested spleen. The ruler indicates millimetre (mm).



Figure 2. Photograph of the opened stomach with presence of a furball and fragments of cockshafers. Insert: Closer view of the isolated cockshafers. The ruler indicates millimeter (mm).



Figure 3. Photograph of the opened large intestine containing abundant soft green faeces admixed with partially digested cockshafers (indicated by the forceps).