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Source: Journal of Feline Medicine and Surgery Open Reports, 6(2)

Published By: SAGE Publishing

URL: https://doi.org/10.1177/2055116920940177 jfms OPEN REPORTS

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*Journal of Feline Medicine and Surgery Open Reports*
1–5


DOI: 10.1177/2055116920940177
journals.sagepub.com/home/jfmsopenreports

This paper was handled and processed by the European Editorial Office (ISFM) for publication in *JFMS Open Reports*

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## Abstract

*Case summary* An adult male intact domestic shorthair cat was presented for acute onset of generalised tremors, stupor, horizontal nystagmus, anisocoria and bilateral absence of pupillary light and palpebral reflexes. Response to intravenous (IV) administration of benzodiazepines was minimal; thus, the induction of general anaesthesia with propofol, midazolam and dexmedetomidine was necessary to control clinical signs. Following a clinical suspicion of neurotoxicosis, a low-dose constant rate infusion (CRI) of IV lipid emulsion (ILE) was started. Phenobarbital and a low-dose CRI of ketamine were also used for neuroprotective purposes. Metaldehyde intoxication was confirmed by qualitative faecal toxicological analysis after discharge. Anaesthetic drugs were progressively tapered and stopped after 28 h and extubation was possible after 44 h. The cat was discharged 8 days after admission with a complete recovery of the clinical signs.

*Relevance and novel information* To the authors' knowledge, this is the first report to describe a case of metaldehyde toxicosis in a cat treated with intensive supportive care and an additional low-dose CRI of ILE.

**Keywords:** Neurotoxicity; lipophilicity; intensive care; decontamination

**Accepted:** 8 June 2020

## Introduction

Metaldehyde is a tetramer of acetaldehyde, a pesticide commonly contained in slug and snail baits.[1] If ingested, it can cause severe neurological signs with tremors, seizures and secondary hyperthermia as the most notable. Metaldehyde intoxication has been reported in many different species, both domestic and wild, such as dogs, horses, livestock and, less frequently, in cats, foxes and humans.[1–2] To our knowledge, only one report of metaldehyde intoxication in two cats is described in the literature.[2]

Intravenous (IV) lipid emulsion (ILE) represents a potential treatment for poisoning from high lipophilic substances such as permethrin, moxidectin, bupivacaine and lidocaine.[3–6] Its mechanism of action seems to be multimodal, including a potential scavenging effect.[7] ILE is usually administered as an IV bolus followed by a constant rate infusion (CRI) in order to create a large lipid-soluble compartment in blood,[7] but no guidelines about doses of ILE infusion during oral toxicosis are available. Recent studies described the use of low-dose ILE infusion,[8,9] in order to prevent potential detrimental effects associated with a huge load of blood lipids.[4,7,10]

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Metaldehyde lipophilicity is low (LogP = 1.1),[11] but it easily crosses the blood–brain barrier and exerts its toxicity on the central nervous system. In the literature, successful use of ILE infusion in the treatment of metaldehyde toxicosis was described in a dog,[12] but no data exist for cats.

We describe a case of metaldehyde toxicity in a cat treated with supportive care and additional use of ILE therapy.

## Case description

An adult male intact domestic shorthair cat, weighing 5.26 kg, was referred to our Veterinary University Hospital for acute onset of generalised tremors. History of exposure was unknown. The cat received endorectal diazepam before admission by the referring veterinarian.

On presentation, the patient was recumbent with generalised fasciculations, hypothermic (rectal body temperature 35.3°C), had a heart rate of 200 beats/min and a respiratory rate of 20 breaths/min. Indirect systolic blood pressure (SBP) (Minidop ES-100VX; Adeco) was 120 mmHg and blood glucose level measured by a blood glucometer (Alphatrack2; Zoetis) was 40 mg/dl. Neurological examination revealed stupor, horizontal nystagmus, anisocoria and bilateral absence of pupillary light reflex and palpebral reflex. An electrocardiogram showed a sinus rhythm. Point-of-care ultrasound was unremarkable. A clinical suspicion of neurotoxicity was first considered, but other differentials could not be excluded.

Initial treatment included an IV bolus of glucose solution (0.50 g/kg) and midazolam (0.2 mg/kg). In order to treat a potential intracranial hypertension, a bolus of hypertonic saline solution (NaCl 7.5%) was administered (4 ml/kg in 20 mins). No significant clinical improvement was observed; thus, a balanced general anaesthesia was induced by IV administration of propofol (Proposure 10 mg/ml [Merial]: bolus 3 mg/kg IV and then a CRI of 0.1–0.25 mg/kg/min) sequentially associated with midazolam (Midazolam IBI 5 mg/ml, bolus 0.2 mg/kg and a CRI of 0.1–0.3 mg/kg/h) and dexmedetomidine (Dextroquillan 0.5 mg/ml [ATI]: CRI of 0.5 µg/kg/h). A low dose CRI of ketamine (Nimatek 100 mg/ml [Dechra], bolus 0.25 mg/kg IV and then a CRI of 0.1–0.2 mg/kg/h) was administered for neuroprotective purposes. During anaesthesia the patient breathed spontaneously with supplemental oxygen at 1 l/min, maintaining a $SpO_2$ of 96–97% and an end-tidal $CO_2$ of 30–45 mmHg. Heart and respiratory rates were within the normal range. Active warming was instituted with a forced-air warmer (Bair Hugger Model 505 Patient Warming System; 3M) to maintain normothermia.

Anticonvulsant therapy with phenobarbital (Luminale 200 mg/ml [Bracco]: 3 mg/kg q12h IM) was then started. Following a clinical suspicion of neurotoxicity, low-dose ILE therapy was started (Intralipid 20% [Fresenius-Kabi]: bolus 1.5 ml/kg IV in 30 mins, then a CRI of 0.25 ml/kg/min for 3 mins, followed by 0.025 ml/kg/min for 6 h, once the maximum dosage of 12.5 ml/kg was reached).[3]

Finally, a gastric lavage was performed, withdrawing dark-green-coloured material, suggesting oral metaldehyde intoxication. Activated charcoal was administered via enemas and a nasogastric tube, and a CRI of metoclopramide was instituted for its prokinetic effect (Vomend 5 mg/ml [Dechra], 1 mg/kg/daily IV). Discoloured, dark-green faeces were submitted for qualitative toxicological analysis with gas chromatography–mass spectrometry. Minimum database abnormalities included compensated metabolic acidosis and hypernatraemia secondary to hypertonic saline solution administration, signs consistent with muscular damage, including increased concentrations of serum creatine kinase and aspartate aminotransferase, and a condition of mild systemic inflammation, supported by neutrophilic leukocytosis and an increased concentration of circulating serum amyloid A protein. Coagulation parameters were within the normal reference intervals (Table 1).

In the first 24 h, the patient presented two suspected episodes of intracranial hypertension characterised by systemic hypertension (SBP 190 mmHg) and miotic pupils, both successfully treated with mannitol (0.5 g/kg IV over 20 mins). Anaesthetic drugs were progressively tapered and stopped after 28 h and extubation was possible 44 h after admission. After 70 h, the chemistry profile was unremarkable except for a mild increase of alanine aminotransferase (ALT). Eight days after admission, complete recovery was seen and the cat started eating autonomously, neurological alterations completely resolved, clinical conditions were assessed as normal and the patient was discharged. Results of toxicological examination confirmed the diagnosis of metaldehyde intoxication.

## Discussion

Metaldehyde is one of the most common molluscicides used for the control of slugs and snails in Europe. Metaldehyde intoxication is a life-threatening condition requiring aggressive treatment of neurological alterations. Its mechanism of action is still unclear, even though evidence suggests that its metabolite acetaldehyde or, more likely, metaldehyde itself can act on the gamma-aminobutyric acid-ergic system.[13] Fatal complications, such as acute respiratory failure or disseminated intravascular coagulation, can occur, with a mortality rate of 16% in dogs.[14–16] Similar data are reported in cats,[17,18] even if information about pharmacological treatment, long-term intoxication effects and prognosis in cats is lacking.[2]

In the case described here, hypothermia, stuporous mentation, generalised fasciculations, horizontal nystagmus and anisocoria were the most remarkable clinical signs at presentation, associated with clinicopathological data supportive of muscular damage and mild

**Table 1** Clinicopathological variables upon hospital admission and at 72 h

| Variable | Hospital admission | 72 h | RI |
|---|---|---|---|
| pH | 7.33 | | 7.34–7.40 |
| $PCO_2$ | 26.4 | | 32.7–44.7 |
| $HCO_3$ | 14 | | 18–23.2 |
| $K^+$ (mmol/l) | 3 | | 3.6–5.8 |
| $Na^+$ (mmol/l) | 161 | | 141–155 |
| $Cl^-$ (mmol/l) | 140 | | 119–132 |
| Anion gap | 10.6 | | |
| Lactate (mmol/l) | 1.6 | | 0–2.0 |
| Haematocrit value (%) | 40.2 | 29.9 | 32–48 |
| Leukocytes (cells $\times 10^3/mm^3$) | 28.22 | 10.74 | 4.80–14.93 |
| Neutrophils (cells $\times 10^3/mm^3$) | 26.60 | 8.11 | 1.60–10.00 |
| Lymphocytes (cells $\times 10^3/mm^3$) | 0.50 | 1.12 | 0.90–5.60 |
| CK (U/l) | 4226 | | 91–326 |
| AST (U/l) | 57 | | 9–40 |
| ALT (U/l) | 46 | 88 | 20–72 |
| Total protein (g/l) | 70.2 | 55.5 | 65.0–88.0 |
| Albumin (g/l) | 30.3 | 20.9 | 26.0–40.0 |
| Creatinine (µmol/l) | 97.24 | 84.86 | 70.72–159.12 |
| SAA (µg/dl) | 22 | | 0–10 |
| PT (s) | 7.3 | | 9–15 |
| aPTT (s) | 14.7 | | 9–20 |

RI = reference interval; $PCO_2$ = partial pressure of carbon dioxide; $HCO_3$ = bicarbonate; CK = creatine kinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; SAA = serum amyloid A; PT = prothrombin time; aPTT = activated partial thromboplastin time

systemic inflammation. Clinical presentation resembled previous reports described in the literature in cats intoxicated with metaldehyde, except for hypothermia, which could be related to previous sedation with benzodiazepines in the present case.[2,13,14] The only case report documenting metaldehyde intoxication in cats dates back to 1978,[2] and few data exist about pharmacological treatments, long-term effects of intoxication and prognosis.

Prompt gastric decontamination, enemas and administration of activated charcoal represent the treatment of choice of the patient intoxicated with metaldehyde, in addition to the control of neurological signs with sedation and muscle relaxation.

Methocarbamol is normally used as the first drug of choice for muscle relaxation in this setting;[13] however, this drug is unavailable in Italy. Balanced general anaesthesia with propofol, midazolam and dexmedetomidine was therefore necessary to control the clinical signs. Phenobarbital was administrated as an anticonvulsant treatment and was associated with a low-dose CRI of ketamine, in order to have a potential neuroprotective effect. Electroencephalogram monitoring was not performed in our patient, but a seizure activity hidden by anaesthetic drugs could not be excluded.[19,20] ILE has been used as an adjunctive treatment for decontamination against several lipophilic toxic compounds both in human and veterinary patients.[3,6,21–23] Its mechanism of action is still under investigation, even if several studies demonstrated its scavenging effect, consisting of the redistribution of lipophilic compound out of toxin-susceptible organs and toward reservoir sites.[7]

The main indication for the use of ILE in clinical practice is reported in cats intoxicated with permethrin, where a faster resolution of clinical signs in treated patients are reported to be within 24 and 48 h.[5,8,22] In permethrin toxicosis, the mortality rate varies from 10% to 22%,[24,25] and survey studies have reported hospitalisation costs as a contributing factor in the decision to euthanase.[25]

Despite the low lipophilicity of metaldehyde (LogP = 1.1),[11] a potential application of the scavenging effect of ILE appeared effective in a case report of a dog with metaldehyde toxicosis.[12] The elimination half-life of metaldehyde is reported to be around 27 h in humans and is associated with prolonged intensive care support.[26] No toxicokinetic data are described in small animals; however, a potential impact of the use of ILE on recovery times and mortality might be considered in companion animals with metaldehyde toxicosis.

In our patient, there was no evidence that ILE influenced recovery time and we could not confirm any temporal association between lipid administration and clinical improvement. However, the presence of a lipid-soluble compartment in blood could have, hypothetically, contributed to a better control of clinical signs. Furthermore, late gastric decontamination and administration of activated charcoal could also have influenced time to resolution of clinical signs.

Potential adverse effects associated with ILE infusion are severe hypertension, acute respiratory distress syndrome,[7,10,27] high lipophilicity of serum[28–30] and 'fat overload syndrome', consisting of liver damage, pancreatitis[28] and fat embolism. Other detrimental effects, such as unilateral facial pruritus, extravasation with pain and local swelling,[31] and suspected corneal lipidosis,[32] are described in the veterinary literature. Even if no optimal protocol of ILE infusion is available, in human medicine the use of a large volume of ILE is described during resuscitation[33,34] and treatment of local anaesthetics, beta blockers or calcium channel blockers overdose.[3,7,35] In veterinary medicine, a maximum total dose of 10 mg/kg after an initial bolus of 1.5 ml/kg is recommended by Fernandez et al,[35] but higher doses are reported for pyrethroid intoxication in cats.[6,23,36] Recent human guidelines and clinical studies recommend the use of low-dose ILE CRI in order to avoid fluid overload or other detrimental effects, with very promising results.[8,9,37] In our case, the infusion of a low dose of ILE was safe with no relevant clinical and clinicopathological alterations, except for serum lipaemia. Hepatic damage secondary to metaldehyde intoxication is widely reported in dogs,[13,14,38] but no data exist for cats. In our patient, a mild increase of ALT, potentially related to administration of phenobarbital and anaesthetic drugs, was reported at 72 h after hospital admission.

## Conclusions

To our knowledge, this is the first report to describe an emergency approach to metaldehyde toxicosis in a cat and the additional use of low-dose ILE as supporting therapy, as carried out previously in dogs.[12] The effectiveness of ILE therapy in our case is unclear because it was necessary to use multiple drugs to control the clinical signs. Further studies are needed to evaluate the possible effectiveness of ILE therapy in metaldehyde intoxication in cats.

**Conflict of interest** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding** The authors received no financial support for the research, authorship, and/or publication of this article.

**Ethical approval** This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

**Informed consent** Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). For any animals or humans individually identifiable within this publication, informed consent (either verbal or written) for their use in the publication was obtained from the people involved.

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