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# Feline permethrin toxicity: retrospective study of 42 cases

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Forty-two cases of feline permethrin toxicity treated at a referral hospital in Sydney, Australia were retrospectively reviewed. In most cases canine permethrin spot-on (PSO) flea products had been directly applied to affected cats. Most presented during summer and there was an increase in cases during the 2007/2008 period. Clinical signs included; tremors/muscle fasciculations (86%), twitches (41%), hyperaesthesia (41%), seizures (33%), pyrexia (29%), ptyalism (24%), ataxia (24%), mydriasis (19%) and temporary blindness (12%). Treatment involved decontamination, anticonvulsants and supportive care. Methocarbamol was not used. Complications occurred in 33% of cats and included: hypothermia (29%), electrolyte abnormalities (26%), aspiration pneumonia (12%), hypoproteinaemia (12%), anaemia (5%), apnoea (7%), respiratory arrest (5%), cardiorespiratory arrest (2%), pleural effusion (2%), urinary tract infection (2%) and corneal ulceration (2%). One cat was euthanased. Feline permethrin toxicity may result in severe clinical signs requiring intensive treatment. Despite prominent label warnings, cases of feline permethrin toxicity continue to occur in Australia and may be fatal.

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Pyrethrins are naturally occurring esters of chrysanthemic acid and pyrethric acid extracted from the flowers of *Tanacetum (Chrysanthemum) cinerariifolium*. Pyrethroids are synthetic analogues of pyrethrins and both substances are neurotoxicants. The major site of action of pyrethrins is at the gated sodium channels in the cell membrane of excitable cells such as nervous tissue and muscle.[1] After an action potential has passed through a cell, pyrethrins bind to and block open a small number of sodium channels in the axonal cell membrane.[2] This causes a reversible prolongation of sodium ion movement into the cell after the action potential has passed. Depolarisation does not occur because impulse conduction is inhibited and this results in repetitive discharging of the cell and clinical signs of toxicity.

Permethrin (3-phenoxybenzyl (1*RS*)-*cis-trans*-3-(2,2-dichlorovinyl)-2,2 dimethylcyclopropanecarboxylate) is a class I pyrethroid insecticide which was first described in 1973.[3] Permethrin has low toxicity in most mammalian species and is commonly used in spot-on pesticide preparations manufactured for flea control.[2]

Pyrethrins and pyrethroids are fat soluble compounds that in most mammals undergo rapid metabolism and excretion after oral or dermal absorption. Following absorption, permethrin is metabolised by hepatic microsomal esterases and oxidases.[4] This is followed by rapid hepatic hydroxylation and conjugation into glucuronides or sulphates which are mainly eliminated in urine.[1] However, cats appear highly sensitive to the effects of permethrin and deficiency of hepatic glucuronosyltransferase has been suggested as a potential explanation for this increased sensitivity.[2]

The clinical signs most commonly reported in cats (and frequency range reported) with permethrin toxicity in the veterinary literature include: seizures/convulsions (11–59%), muscle fasciculations/tremors (10–58%), twitching (22–35.3%), shaking/shivering (10%), ptyalism (6.5–22.7%), hyperaesthesia (7–12.2%), ataxia/inco-ordination (6.5–22%), pyrexia (10–15%) and mydriasis (14.3–19%).[2–9] Other clinical signs less commonly reported include: ear flicking, paw shaking, repeated contractions of cutaneous muscles (distinct to muscle fasciculations), vomiting, diarrhoea, anorexia, lethargy, anxiety, disorientation/confusion, hallucinations, temporary blindness, head tilt, hypothermia, lacrimation, urinary retention,

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cyanosis, collapse, coma, tachypnoea, dyspnoea, respiratory arrest, cardiac arrhythmias and cardiac arrest.[4,6–8,10]

The onset of clinical signs following exposure to a permethrin spot-on (PSO) is usually within a few hours but may be delayed up to 24–72 h.[3,4] There is no reported correlation between the amount of permethrin applied and the severity of clinical signs induced. Even small quantities of PSO have been reported to result in severe toxicity in the cat where the $LD_{50}$ has not been determined.[2,3] Haematological and biochemical values are usually reported to be normal. In cats that recover following treatment, clinical signs usually resolve within 24–72 h but may take longer.[2,4,5]

Diagnosis of feline permethrin toxicity is usually based on a history of recent permethrin exposure and development of typical clinical signs. Differential diagnoses include other causes of tremors and seizures (see Table 1).

Recommended treatments focus on early seizure control, decontamination and supportive care of intoxicated cats. Drugs used for control of seizures and tremors reported in the literature include methocarbamol (a centrally acting muscle relaxant), benzodiazepines, barbiturates, inhalant anaesthetics and propofol.[3,8,9,11]

Dermal decontamination involves washing thoroughly in lukewarm water with a mild hand dishwashing detergent. Hot water may increase dermal perfusion and absorption of permethrin, while cold water may exacerbate toxicity as lower temperatures may cause an increase in activity of permethrin at the cell membrane sodium channel.[1,8] In the case of recent (less than 1 h) oral exposure, decontamination may include induction of emesis in suitably selected cats, activated charcoal and a cathartic.[1,10] Supportive care for intoxicated cats includes the use of intravenous (IV) fluids, body temperature management and nursing care.

The American Society for Prevention of Cruelty to Animals (ASPCA) Animal Poisons Control Centre (APCC) listed permethrin toxicity as one of the 10 most common feline toxicities reported between 2002 and 2005.[12] The Veterinary Poisons Information Service (VPIS), London records permethrin intoxication as the most common toxicological cause of feline deaths reported.[7]

There are reviews in the veterinary literature detailing the incidence and mortality rates of feline permethrin toxicity in Australia, the UK and the USA recorded by poisons information or adverse reaction reporting services (see Table 2).[3,4,6,7,9,13] Most reports relate to concentrated canine PSO product use on cats. Although permethrin toxicity is well recognised in cats, its true incidence may be underestimated because not all toxic events are reported by veterinarians to poisons information or adverse reaction reporting services. Few reports detail the clinical management, treatment and complications associated with toxicity and these are usually limited to single case descriptions.[2,9,14]

**Table 1**. Potential causes of tremors and seizures in cats.

| |
|---|
| Lead toxicity |
| Encephalitis |
| Idiopathic seizures ('epilepsy') |
| Hypoglycaemia |
| Hypocalcaemia |
| Hepatic encephalopathy |
| Head trauma |
| Strychnine poisoning |
| Ingestion of over-the-counter human medications such as pseudoephedrine, or illicit substances such as amphetamines |
| Bromethalin rodenticides |
| Tremorgenic mycotoxins |

## Materials and methods

A retrospective study was performed using the clinical records of the Animal Referral Hospital (ARH) in Sydney Australia, a small animal referral and emergency centre. Records were reviewed from January 2000 to May 2008. Cats were included that had confirmed recent permethrin exposure.

## Results

### *Signalment and clinical signs*

During this period, 42 cats presented following permethrin exposure. Sixty percent of cases occurred in the 2007/08 period covered by the study (2000: 1; 2001: 3; 2002: 4; 2003: 0; 2004: 3; 2005: 3; 2006: 3; 2007: 17; 2008: 8).

The number of cats that presented following permethrin exposure varied seasonally. Twenty-five cats (59.5%) presented in the summer (December–February); 12 cats (28.6%) presented in autumn (March–May); four cats (9.5%) presented in spring (September–November); and one cat (2.4%) in winter (June–August).

The brand of PSO product applied was recorded for 31 cats (Table 3) and 10 cats had an unidentified brand applied. In 41 cats a PSO product manufactured for use on dogs was applied. One cat had a permethrin household flea spray product applied. In eight cases the PSO was identified as being intended for large dogs, one was intended for medium dogs and five were intended for small dogs. Eight cases were described as involving less than a full tube applied to the cat. In three cases the owner divided a tube between two to four animals (dogs and cats). None of the cases reported in this series were reported as adverse drug events to the regulator Australian

**Table 2**. Summary of some published reports of feline permethrin toxicity.

| Reference/organisation | Number of cats | Number of cats with toxicity | PSO applied directly | Contact with dog | Other route of exposure | Survival rate | Death rate | Euthanased | Overall mortality rate |
|---|---|---|---|---|---|---|---|---|---|
| Gray[6] UK suspected adverse reaction surveillance scheme, veterinary medicines directorate | 27 (18 incidents) | 27 (100%) | – | 2/18 incidents (11%) | – | 17/27 (63%) | – | – | 10/27 (37%) |
| Sutton et al[7] VPIS (UK) | 286 | 277 (96.9%) | – | – | – | 247/277 (89.2%) | 20/277 (7.2%) | 10/277 (3.6%) | 30/277 (10.8%) |
| Dymond and Swift[9] (Australia) | 20 | 20 | 17/20 (85%) | – | 3 following environmental exposure | 19/20 (95%) | 1/20 (5%) | – | 1/20 (5%) |
| Linnett[4] Australian pesticides and veterinary medicines authority's adverse experience reporting program | 26 incidents | 26 incidents | 22 (75%) | 25% | 1 cat licked an empty permethrin containing packet | 77% | – | – | 23% |
| Woo and Lunn[14] (Australia) | 1 | 1 | 1 | – | – | yes | – | – | – |
| Richardson[2] (United States) | 1 | 1 | 1 | – | – | yes | – | – | – |
| Meyer[3] (United States) pharmacopoeia veterinary practitioners' reporting program | 12 | 12 | 11 | 1 | – | 8/11 (72.7%) Outcome unknown 1 cat | 4/11 (36.4%) | – | 4/11 (36.4%) |
| Meyer[3] Environmental protection agency's incident data system (United States) | 149 | 149 | 125/149 (84%) | 24/149 (16%) | – | 48/87 (55%) Outcome unknown 62 cats | – | – | 39/87 (45%) |

**Table 3**. PSO products recorded as applied to affected cats in this series.

| Product name | Active constituent(s) | Manufacturer | Date of registration* | Number of affected cats | Year applied (*n*) |
|---|---|---|---|---|---|
| Advantix for dogs | 100 g/l imidacloprid, 500 g/l permethrin (40:60 cis:trans) | Bayer Australia (Animal Health) | 30/3/2005 | 7 | 2006 (1); 2007 (4); 2008 (2) |
| Exelpet flea and tick liquidator SG for dogs and puppies | 650 g/l permethrin (40:60 cis:trans) | Effem Foods T/A Masterfoods Australia and NZ | 7/9/2006 | 12 | 2006 (1); 2007 (7); 2008 (4) |
| Exetick NF tick and flea insecticide for dogs and puppies | 650 g/l permethrin (40:60 cis:trans) | Schering-Plough | 27/3/2003 | 1 | 2002 (1) |
| Friskies total life cycle flea eliminator line-on for dogs | 3 g/l pyriproxyfen, 400 g/l permethrin (40:60 cis:trans) | Virbac (Australia) | 28/7/1999 | 11 | 2001 (3); 2002 (3); 2004 (1); 2005 (1); 2006 (1); 2007 (2); 2008 (4) |

*Source: http://www.apvma.gov.au/gazette/subpage_gazette.shtml

Pesticides and Veterinary Medicines Authority (APVMA). This lack of reporting was mainly a consequence of ignorance, with few veterinarians aware of the reporting process for adverse events.

In 39 cases the owner of the cat directly applied the PSO/spray. In two cases the owner confused separate dog and cat flea spot-on products that they had at home and applied the incorrect product to each species. In three cases the product was applied to a dog that lived with the cat. However, it was not recorded whether or not the treated dogs and untreated cats were separated for any period after application.

Twenty-six of the cats were domestic shorthairs and five were domestic longhairs. Eleven cats were pedigree or pedigree crosses; Birman (one), Birman cross (one), Burmese (two), Burmilla (one), Himalayan cross (one), Persian (one), Persian cross (one), Ragdoll (two) and Russian Blue (one).

Age was recorded for 39 cats. The median age was 2 years, the mean age was 3 years and the age range was 2 months−15 years old. There was no sex bias in the group. There were eight male entire, five female entire, 15 female neuter and 13 male neuter cats. The sex of one cat was not recorded. Body weight was recorded for 29 cats. Median weight was 4 kg (mean 3.9 kg; range 0.7−6.2 kg).

Time from application to onset of first observed clinical sign was recorded for 22 cats. Median time for onset of clinical signs after application was 8 h (mean 10 h; range 1−42 h). Only approximate times were recorded for a further 10 cats. One cat was described as having the product applied the day before. Of cats that developed signs following permethrin application to dogs in the same household, one developed signs 6 h after it was applied to the dog and two developed clinical signs the day after application to the dog.

Time from first onset of clinical signs to presentation was recorded for 20 cats. Median time to presentation was 1.25 h (mean 2 h; range 0−10 h). One cat presented 1.5 h after application when the owner realised they had mistakenly applied a dog permethrin product, 7 h before clinical signs started.

The most common clinical signs described included tremors/muscle fasciculations (36 cats; 86%), twitches (17; 41%), hyperaesthesia (17; 41%), seizures (14; 33%), pyrexia (12; 29%), ptyalism (10; 24%), ataxia (10; 24%), mydriasis (8; 19%) and temporary blindness (5; 12%). Less common clinical signs included vocalisation (two), anxiety (two), tachypnoea (one), vomiting (one), and anorexia (one). One cat exhibited local hyperaesthesia, rubbing at the left ear adjacent to where the product was applied. Another cat had a permethrin product applied by the owner and presented with lameness and suspected permethrin toxicity. The cat was washed and did not develop typical clinical signs of toxicity.

Twenty-nine of 36 cats with tremors were described as having generalised tremors/muscle fasciculations.

Six cats were described as having fine tremors, four were described as having mild to moderate tremors and two were described as having moderate to marked tremors.

Nineteen of 36 cats with tremoring/muscle fasciculations had duration of tremoring recorded. Tremors were present for a median of 30 h (mean 35 h; range 4.5–79 h). Eleven cats had tremors for an unrecorded period of time (one of which was discharged after 24 h of treatment with fine residual tremors present). Five cats had only approximate times spent tremoring recorded and one cat had tremors for 61 h before it was euthanased.

Fourteen of 17 cats with twitches were also described as having tremors. Of the 17 cats, two cats had generalised twitching, seven had ear and/or facial twitching (four of these cats had this as their final clinical sign before resolution) and eight cats had undefined twitches. Twitching times were recorded for five cats (median 61 h; mean 54 h; range 24–79 h).

Eleven of 17 cats with hyperaesthesia were described as having clinical signs that worsened with physical and/or light and/or sound stimulation. Of 14 cats that seizured, four were described as presenting in status epilepticus and four had multiple seizures.

Temperature (degrees Celsius; °C) at presentation was recorded for 31 cats. Median temperature was 39.2°C (mean 39.0°C; range 37.2–40.4°C). Of 12 cats with pyrexia (temperature $\geq$39.5°C), four had tremors, three had tremors/seizures, three had tremors/twitches and one had tremors/twitches and a seizure.

Ataxia was described in 10 cats at presentation (unable to stand/walk (three), marked ataxia (one) and mild ataxia (one)). Six cats were described as ataxic during their recovery period when medical therapy was being withdrawn.

Eight cats were described as having mydriatic pupils. One cat had miotic pupils at presentation and was ultimately euthanased.

### Treatment

Various treatment regimes were used depending on the severity of clinical signs, response to initial therapy and clinician preference. The most common drug treatments used were initial IV diazepam (33 cats) and IV phenobarbitone (23 cats), followed by midazolam constant rate infusion (CRI) (17 cats) and/or propofol CRI (15 cats) (if required). The majority of cats were bathed, and received IV fluids.

Decontamination procedures described included bathing with hand dishwashing detergent and gastrointestinal decontamination. Thirty-seven cats were recorded as being bathed (23 by the veterinarian; 13 by the owner and then repeated by the veterinarian; and one only by the owner). Two cats were not bathed, both of which had been exposed following PSO application to dogs in the same household. Activated charcoal was given to four cats either orally (two cats) or via stomach tube (two cats). All four cats had been exposed cutaneously to permethrin products >12 h previously.

Diazepam was given to 33 cats. At presentation 27 cats received IV diazepam and two also received it per rectum. One cat continued on oral diazepam and six cats received diazepam by an unrecorded route. Seventeen cats received more than one dose of diazepam in the first 24 h and one cat stayed on diazepam for a total of 7 days (oral for 4 days). Exact doses given were recorded for 20 cats. The median IV dose was 0.47 mg/kg (mean 0.47 mg/kg; range 0.13–1.5 mg/kg). The two per rectum doses used were 0.47 and 1.7 mg/kg.

Phenobarbitone was given to 23 cats (IV to 21 cats and per rectum to two cats). The dose of phenobarbitone given was recorded for 19 cats. The median IV dose was 4 mg/kg (mean 4.1 mg/kg; range 2–8 mg/kg) and per rectum dose was 6 mg/kg. Four of the cats received two or three doses of phenobarbitone and the rest only one initial dose.

Midazolam was given to 17 cats. Sixteen cats were placed on midazolam CRIs and two of them received an initial IV bolus. One cat was given a single IV dose (0.2 mg/kg) and then became hyperexcitable/dysphoric and was placed on a propofol CRI. Fourteen cats had midazolam CRI doses recorded. Median IV CRI dose was 0.18 mg/kg/h (mean 0.2 mg/kg/h; range 0.05–0.31 mg/kg/h). Twelve cats on midazolam CRIs received concurrent propofol CRIs using a second IV site. One cat on a midazolam CRI received intermittent propofol boluses. Midazolam CRI duration was recorded for 14 cats. The median midazolam CRI duration was 38.5 h (mean 41.9 h; range 9–115 h). Typically the midazolam CRI was continued after the propofol CRI was stopped and then weaned off.

Propofol was given to 15 cats. Of these, 14 received propofol CRIs and one received IV boluses. Thirteen cats had propofol doses recorded. Median propofol CRI dose was 6.8 mg/kg/h (mean 7.4 mg/kg/h; range 1.5–19 mg/kg/h). Propofol CRI duration was recorded for 14 cats. The median propofol CRI duration was 23 h (mean 26.4 h; range 1–72 h). The single cat that received IV propofol boluses was given them over the first 8 h of treatment.

Pentobarbitone was given intravenously to five cats by referring veterinarians either prior to referral (four cats) or after transfer from the ARH emergency service (one cat). All cats had good to profound sedation on pentobarbitone and adverse clinical signs ceased. One cat experienced apnoea both while on a propofol CRI and then under isoflurane anaesthesia at the ARH and was given pentobarbitone following this for 3 days at the referring veterinary clinic. The four other cats were given pentobarbitone following poor initial response to sedation with diazepam (one cat), diazepam/phenobarbitone (two cats) or diazepam/acepromazine (one cat).

IV fluids were given to 36 cats and one cat received subcutaneous fluids (SC) fluids. Median duration of

fluid therapy was 44 h (mean 64 h; range 12–264 h). An IV colloid (Dextrans 70) was given to three cats at a rate of 1 ml/kg/h while receiving concurrent crystalloids to provide oncotic support. All three cats had hypoproteinaemia secondary to hypoalbuminaemia. They received colloids for 55, 92 and 240 h, respectively.

Adjunctive sedative drugs were used in 12 cats. This included buprenorphine (one), acepromazine (one), butorphanol (three), acepromazine/butorphanol (one) and acepromazine/morphine (six). Most cats received more than one dose (mean 6 doses; median 3 doses; range 1–30 doses). All cats also received other sedatives (midazolam (one cat), midazolam/propofol (three cats), diazepam/pentobarbitone (one cat) or diazepam/phenobarbitone/midazolam/propofol (five cats)).

Effect of initial sedation at presentation (acepromazine, buprenorphine, butorphanol, diazepam, morphine, phenobarbitone or combinations) was described for 27 cats. It was reported as poor (little to no reduction in clinical signs) for 14 cats, moderate (suppression of clinical signs but requiring repeat doses) for seven cats and good (resolution/suppression of clinical signs) for six cats.

Atropine was given to eight cats. Doses of 0.02–0.5 mg/kg were used in three cats and were not recorded for five cats. Six cats received atropine at presentation and then for variable periods afterwards. Two cats received atropine following cardiorespiratory arrest or respiratory arrest/bradycardic episodes.

Miscellaneous medications given included medetomidine (one cat to no effect), alfaxalone (one cat at presentation intramuscularly to allow IV catheter placement), prednisolone sodium succinate (one cat), adrenaline (one cat after cardiorespiratory arrest) and isoflurane (one cat for 6 h).

Endotracheal (ET) tubes were used for 12 cats during propofol CRIs. Median duration of intubation was 24 h (mean 23.5 h; range from 1 to 60 h). One cat was intubated for 19 h prior to euthanasia. All intubated cats received ET care including suctioning of tubes/humidification q4 h and tube changing q8–12 h. Cats that were intubated had end tidal carbon dioxide concentrations monitored in addition to oxygen saturation and blood pressure.

Manual ventilation was required for three cats during treatment (two temporarily following respiratory or cardiorespiratory arrest, and one intermittently during the first several hours of propofol sedation). Two cats required mechanical ventilation due to inadequate ventilation or apnoea under propofol CRIs for 15 h and <12 h, respectively. One of these cats had suspected aspiration pneumonia and both survived to discharge.

Supplemental oxygen was given to 13 cats. Ten of these cats had oxygen via ET tube (seven of which continued oxygen after extubation via mask/nasal or box routes). Two cats received oxygen by mask and one via oxygen box. All cats that received oxygen via ET tube or mask were on propofol CRIs. Median duration of oxygen therapy was 38 h (mean 46.7 h; range 4–96 h). Cats receiving oxygen supplementation had oxygen saturation measured.

Supplemental heating was reported for 16 cats (hot water bottles, heat mats, Bair hugger, bubble wrap, blankets or combinations) to maintain normothermia. Of these cats, 11 were on propofol CRIs and three had received pentobarbitone.

Indwelling urinary catheters were placed in 10 cats, all of which received propofol CRIs and nine of which were also intubated. Manual bladder expression was performed on four cats, two of which received pentobarbitone and two of which received propofol CRIs.

Injectable antibiotics were given to 14 cats (cephazolin, enrofloxacin, trimethoprim/sulfadiazine, amoxicillin–clavulanate, ticarcillin–clavulanate or combinations). Ten of these cats continued with oral antibiotics (cephalexin, trimethoprim/sulfadiazine, amoxicillin–clavulanate, orbifloxacin or combinations). Twelve of the cats had ET tubes (one of which vomited or regurgitated), 10 had indwelling urinary catheters placed (all but one of these had an ET tube). Five cats given antibiotics had suspected aspiration pneumonia and one had a urinary tract infection after having an indwelling urinary catheter for 6 days.

Hospitalisation times were recorded for 34 cats. Median hospitalisation time was 2 days (mean 3 days; range 0.5–11 days).

### Complications

Complications during treatment occurred in 14 cats (33%), most of which had more severe clinical signs that required intensive management. Complications included hypothermia (12 cats), electrolyte abnormalities (11 cats), aspiration pneumonia (five cats), hypoproteinaemia (five cats), anaemia (two cats), apnoea (three cats), respiratory arrest (two cats), cardiorespiratory arrest (one cat), pleural effusion (one cat), urinary tract infection (one cat) and corneal ulceration (one cat).

During treatment there were 13 hypothermic episodes involving 12 cats (29%) (temperature mean 34.4°C; median 35°C; range 32.2–36.4°C). Of these episodes, one occurred during pentobarbitone sedation, two occurred following bathing and pentobarbitone sedation, five occurred during propofol CRIs, four occurred following bathing and propofol CRIs and one cat (temperature 32.2°C) developed hypothermia following bathing/sedation and cardiorespiratory arrest. One cat developed iatrogenic hyperthermia following overzealous external warming to correct hypothermia during propofol CRI.

Aspiration pneumonia was suspected in five cats during treatment. All five cats had propofol CRIs and ET tubes placed with median tube placement times of 32 h (mean 34 h; range 19–60 h). Four of these cats had thoracic radiographs taken and four had ET

tube cultures performed. Radiographic findings included right cranial lung lobe consolidation, left cranial lung lobe consolidation, left cranial and caudal lung lobe consolidation and mixed generalised alveolar interstitial pattern. ET tube cultures were performed in a total of six cats while intubated, and these yielded *Pasteurella* species (three), *Enterobacter* species (one), *Enterococcus* species and *Serratia* species (one), and *Enterococcus* species and *Klebsiella* species (one).

Apnoea was reported for three cats. Two cats experienced apnoea during propofol CRIs and one cat had apnoea both during propofol CRI and isoflurane anaesthesia. One cat experienced respiratory arrest and bradycardia following initial propofol administration. Another cat experienced respiratory arrest and was eventually euthanased. A third cat experienced cardiorespiratory arrest soon after admission and administration of alfaxalone intramuscularly, two propofol boluses and a CRI, midazolam CRI and IV diazepam and was successfully resuscitated.

Biochemical and/or haematological blood testing was performed for 20 cats. Abnormalities detected at presentation and during hospitalisation included mild to moderate increases in alanine aminotransferase (two cats), mild increase in creatinine (one cat), mild hyponatraemia (six cats), moderate hyponatraemia (one cat), mild hypochloraemia (two cats), mild to moderate hypokalaemia (four cats), marked hypokalaemia (two cats) and marked hyperkalaemia (one cat). Two cats developed mild anaemia during treatment.

Five cats had hypoproteinaemia which was first detected on day 1 (two cats) or day 2 (three cats). Three of the cats had mild to marked hypoalbuminaemia. The five hypoproteinaemic cats all had severe clinical signs including generalised tremors (one presented in status epilepticus). They were hospitalised for 3 (prior to euthanasia), 4, 7, 8 and 11 days, respectively. This was compared to a mean of 3 days and median of 2 days for the 34 cases as a whole where hospitalisation times were recorded. The hypoproteinaemic cats all required midazolam and propofol CRIs to control clinical signs. One cat had ammonia and resting bile acids checked which were within normal limits. Post prandial bile acids performed on day 8 were also normal.

Haematuria and a urinary tract infection occurred in one cat following 6 days of catheterisation with an indwelling urinary catheter. One cat developed a superficial corneal ulcer following propofol CRI.

Temporary blindness was described in five cats. All five cats received midazolam CRIs and four received concurrent propofol CRIs. Four of the cats were described as blind after general anaesthesia/sedation was discontinued. These cats were described as having reduced (one cat) or absent menace (four cats). One cat was described as bumping into objects. Three cats were recorded as having vision again after 1, 4 or 6 days.

Thirty-four cats were recorded as surviving to discharge. Follow-up beyond discharge was available for 11 cats. Follow-up periods ranged from 11 days to 65 months, with a mean of 16 months and a median of 5 months. Ten were reported to be normal and one cat was reported to be 80% back to normal behaviour at day 16 on follow-up. An additional cat that developed severe hypoalbuminaemia was discharged but did not have follow-up information available beyond day 15. Records of outcome were incomplete for seven cats.

The cat that was euthanased in this study was a 4-year-old male neutered domestic shorthair. Generalised tremors and twitches occurred 6 h after an Advantix small dog tube was applied to a dog in the same household that the cat played with. There was no recorded delay in seeking veterinary attention. At presentation the cat had miotic pupils and a temperature of 39.8°C. The cat was not bathed as exposure was suspected to be oral ingestion off the dog. At presentation a blood panel including urea, creatinine, ALT, ALP, total bilirubin, total protein, electrolytes, lactate and creatine kinase were performed and were normal. Potassium was mildly decreased at presentation. The cat was treated with a midazolam and propofol CRI to control tremors, with low dose sedation with either butorphanol or acepromazine and morphine sedation to reduce CRI doses. A closed urine collection system was placed.

Severe hypoproteinaemia (38 g/l; 57–89), hypoalbuminaemia (13 g/l; 22–40) and hyperkalaemia (9.6 mmol/l; 3.5–5.8) developed on day 2. Hyperkalaemia secondary to muscle damage from the tremors was suspected. The cat developed a hyperkalaemia associated cardiac arrhythmia and was treated with calcium gluconate, regular insulin and dextrose. The potassium levels reduced to the normal range (4.2 mmol/l; 3.5–5.8) by 10 h after detection of hyperkalaemia. Thoracic radiographs revealed a generalised alveolar interstitial pattern and aspiration pneumonia was suspected. In house cytology was suggestive of bacterial pneumonia. Antimicrobial treatment with enrofloxacin and cephazolin was started. ET tube culture revealed moderate growth of *Enterococcus* species and heavy growth of *Klebsiella* species. Mechanical ventilation was required soon after with respiratory arrest. Euthanasia was requested with persistent tremors requiring medical intervention 61 h after admission and deteriorating lung function.

## Discussion

Cats that presented following permethrin exposure in this study were young, with a mean of 3 years, median of 2 years and range of 2 months to 15 years old. Two previous Australian studies also found similar age distributions. Dymond and Swift[9] reported 20 cases with a mean age of 4 years and a range of 3 months to 10 years. Linnet[4] reported that almost two-thirds of cases involved cats that were 1 year

old or less. A recent cross-sectional survey of the Sydney pet cat population reported a mean age of 7 years and a median age of 6 years.[15] Whittem[1] refers to 87 cases of permethrin toxicity where all intoxicated cats were younger than 4 years of age and more than half of the cats were less than 12 months old. Over-representation of young cats with permethrin toxicity has not been previously reported and may be due to the small sample sizes of the studies.

Domestic cross-bred cats appeared to be over-represented (74%) compared to the hospital population (70%) over the same time period. However, the domestic cross-bred cat prevalence was similar to a recent cross-sectional survey of the Sydney pet cat population (77%).[15] These differences may be due to the small sample size of the study or may reflect socioeconomic groups of owners. For example, owners of domestic cross-bred cats may be more likely to purchase supermarket brand flea products. The lower domestic cross-bred cat prevalence in our patient population may reflect referral centre biases.

There was variation in the time of year that cats presented with permethrin toxicity with most cats presenting in summer and autumn. This distribution likely corresponds to seasonal variations in flea population and flea product use in Sydney. A seasonal variation has also been reported in the UK by the VPIS with an increase in inquiries from June to July and a peak between August and October.[7]

Sixty percent of cases occurred in the 2007/08 period covered by the study. Veterinary permethrin containing products for dogs have been available on the Australian market since 1999. However, PSO preparations have become increasingly popular, with many of these products available in supermarket stores. Approximately half of the cats (24/41) were recorded to have developed toxicity following the use of a PSO product obtained from a supermarket. Easy access to PSO products and lack of owner compliance with label directions played a role in the poisoning of many of our cases.

The clinical signs described by veterinarians for the cats included in this study are similar to those previously reported in the literature. The incidence of seizures (33%), ptyalism (24%), ataxia (24%) and mydriasis (19%) fell within or close to previously reported ranges.[2–9] The incidence of some clinical signs was higher than previously reported ranges. These included tremors/muscle fasciculations (86% compared to 10–58%), twitching (41% compared to 22–35%), hyperaesthesia (41% compared to 7–12%) and pyrexia (29% compared to 10–15%). No cats presented to the ARH were described to be shaking or shivering. These differences may be due to the small sample size of the study, clinician differences in interpreting/describing clinical signs (for example, the terms tremors, twitches or shaking could be used to describe the same clinical sign) and referral centre patient bias (cats with more severe clinical signs may be more likely to be referred to a specialist/emergency hospital, in this study six cats (14%) were referred).

Hypothermia was the most common complication encountered during treatment occurring in 29% of cats. Dymond and Swift[9] reported hypothermia following bathing in 88% of cats treated. Careful monitoring and management is required to maintain normothermia because hypothermia may exacerbate toxicity by causing an increase in the activity of permethrin at the cell membrane sodium channel, though internal body temperatures below 25°C may be necessary to accentuate the adverse affects of pyrethroids.[18] Cats that presented with pyrexia in this study did not require active cooling because body temperature reduced with bathing and control of clinical signs.

Blindness has occasionally been reported in cats with permethrin toxicity. Gray[6] reported blindness in two cats. Sutton, Bates and Campbell[13] reported temporary blindness in three cats. Linnett[4] reported temporary blindness in an unspecified number of cats. Temporary blindness occurred in five cats (12%) during hospitalisation in this study. All five cats received midazolam CRIs and four also received propofol CRIs. The four cats that received propofol CRIs had blindness recorded after the CRIs were discontinued. Three cats were described with vision again after 1, 4 or 6 days, respectively. Three of these cats had anaesthetic complications including apnoea (two cats) and hypoventilation (one cat). One of these cats developed miotic pupils following the episode of apnoea and was treated with mannitol for suspected increased intracranial pressure. Another cat presented in status epilepticus and another had altered mentation combined with blindness and a prolonged anaesthetic recovery over 2–3 days. Three cats with temporary blindness were hypoproteinaemic. It is possible that the clinical signs they displayed when sedative/anaesthetic medications were discontinued were due to prolonged action of highly protein bound drugs (midazolam and propofol) or episodes of hypoxia.

To the authors' knowledge this is only the second detailed report of treatment of a series of cases of feline permethrin toxicity and the first to describe a series of cats treated without the use of methocarbamol. Treatment of feline permethrin toxicity with IV methocarbamol is widely recommended in the veterinary literature (55–220 mg/kg up to 330 mg/kg/day, give half the dose rapidly, not exceeding 200 mg/min and then the rest to effect).[2,3,8,12] However, in Australia during the study period, methocarbamol was only available in a human oral tablet formulation. Oral tablet administration may not be safe in cats with severe tremors or seizures. Sutton et al[7] suggested crushing methocarbamol tablets and administering to sedated cats via stomach tube in cases refractory to other seizure/tremor control treatments. Dymond and Swift[9] described for the first time six cats that received crushed methocarbamol tablets in

saline per rectum via a feeding tube then orally when they were able to swallow. All of their cases were initially stabilised with diazepam or propofol (ie, given methocarbamol when clinical signs were reduced towards the end of their clinical phase). They reported no difference in the duration of treatment of methocarbamol versus non-methocarbamol treated cats. However, cats that received methocarbamol did not require further treatment with diazepam or propofol. Evaluation of the use of methocarbamol via IV, per os (PO) or per rectum routes compared to non-methocarbamol treated cats involving a larger number of cats is required.

Tremoring times and overall hospitalisation times for the cats in this study are similar to previous reports with an average tremoring time of 35 h (range 4.5–79 h) and an average hospitalisation time of 3 days (range 0.5–11 days).[2,4,7]

Eight cats received acepromazine in combination with other medications during treatment and six cats received atropine at presentation. Atropine is not an antidote for permethrin toxicity, and is not recommended. Although outcome was not adversely affected in cats receiving acepromazine in this study, we would caution against its use in permethrin affected cats as acepromazine may induce adverse effects due to extrapyramidal stimulation by pyrethrins and pyrethroids.[12,16]

In this study 33 cats received diazepam and 17 cats received midazolam as part of their initial stabilisation and ongoing treatment. One cat became hyperexcitable and dysphoric following 0.2 mg/kg midazolam IV. This resolved when the cat was started on a propofol CRI. Martin and Campbell[5] reported paradoxical exacerbation of neurological signs in some cats with permethrin toxicity treated with diazepam. These cats were then treated with acepromazine (which should be used cautiously) or barbiturates.

A localised cutaneous hyperaesthesia syndrome following dermal application of permethrin or other pyrethroids has been described in humans. Symptoms include stinging or burning sensations that progress to numbness after a delay of minutes to hours.[8,10] In this study, one cat presented 12 h after application of a PSO to the skin behind the left ear. The owner described the cat as furiously rubbing the left ear and placing it on the bathroom floor tiles. The cat was bathed and discharged with no other clinical signs after 12 h of hospitalisation. Cutaneous hyperaesthesia has been suggested to possibly occur in cats and may have contributed to the clinical presentation in this case.[10]

The hypoproteinaemia detected in five cats and concurrent hypoalbuminaemia in three cats may have had multifactorial causes. Fluid therapy resulting in haemodilution and repeated venepuncture for blood collection to monitor critical patients may have contributed. However, all five cats had evidence of hypoproteinaemia early in the course of treatment and in two cases this was detected at presentation. All five cats had severe clinical signs of permethrin toxicity at presentation and we speculate that severe tremors/seizures may have resulted in protein leakage from the vascular space in these cats. There was no evidence of gastrointestinal loss or reduced hepatic function in these cats.

Aspiration pneumonia was suspected in five cats during treatment. All five cats had propofol CRIs and ET tubes placed. The duration of intubation for these five cats was longer than for most cats in the study, likely reflecting the severity of their clinical signs. Cats that are recumbent for prolonged periods should be carefully monitored for complications such as aspiration pneumonia.

One of 42 cats (2%) was euthanased. Follow-up to discharge was not available for seven cats. One cat died in a recently published study of 20 permethrin poisoned cats treated intensively at an emergency centre in Brisbane, Australia.[9] Of seven other published retrospective studies of feline permethrin toxicity from Australia, the UK and the USA, only five provide mortality rates (see Table 2) which range from 11 to 37%. Some of these studies did not have outcomes recorded for large numbers of cats or did not differentiate between cats that died or were euthanased. Many of these studies did not provide reasons for death or euthanasia or describe specific treatments given to cats that died or complications that arose. These retrospective studies were all based on data collected by poisons information services or adverse reaction reporting services. The cases reported to these organisations may be biased towards more severely affected cases or cases where mortality has occurred (ie, veterinarians and owners may be more likely to report or seek advice for severe or fatal cases). This study and the retrospective study reported by Dymond and Swift[9] may also be biased towards more severely affected cases that presented to emergency and referral hospitals.

Four owners of cats that presented with clinical signs of permethrin toxicity also had another cat at home that had been treated with a PSO product at the same time. Of these four additional cats, two cats developed no clinical signs, one cat developed mild tremors 19 h after application and was treated by the referring veterinarian exclusively, and one cat was found dead 12 h after application. Two owners also reported previous use of permethrin containing spot-on products on their cats without the development of clinical signs.

In this study 34 cats were recorded as surviving to discharge. Ten of eleven cats where follow-up beyond discharge was available were reported to be normal. Dymond and Smith[9] reported that 19 cats that survived to discharge were normal at follow-up after 3 months. Other studies of permethrin toxicity in the literature report a low incidence of permanent sequelae in surviving cats following treatment. However, they do not specify the actual complication rate or detail the type of complications that occur.[4,7,17]

**Table 4**. Recommendations for management of feline permethrin toxicity*.

Veterinary treatment plan:

**1. Seizure control**

(i) Diazepam: 0.25−0.5 mg/kg IV (can also be given per rectum), repeat PRN q3−5 min

(ii) Midazolam: 0.3 mg/kg IV/IM, repeat PRN q3−5 min

If ongoing seizures after benzodiazepine bolus × 2, then consider:

(iii) Propofol: 4−6 mg/kg slow IV as a bolus, then 0.05−0.3 mg/kg per min IV as a CRI

(iv) Alfaxalone CD: 2−3 mg/kg slow IV bolus

(v) Phenobarbitone: 2−4 mg/kg slow IV, diluted 1:10 with 0.9% NaCl. Repeat PRN q2 h, total dose should not exceed 20 mg/kg/day

**2. Muscle fasciculation control** − Note that the aim is not to completely anaesthetise the patient, but to decrease the severity of clinical signs.

(i) Methocarbamol (if available): 55−200 mg/kg IV/PO tid, up to a maximum dose of 330 mg/kg per day

(ii) Midazolam: 0.002−0.005 mg/kg per min h IV as a CRI

(iii) Propofol: 0.05−0.3 mg/kg per min IV as a CRI

**3. Ensure patent airway**. Swab/suction pharynx if hypersalivating. Provide oxygen support if needed (maintain $Sp0_2$ >95%).

**4. Skin decontamination**. Warm bath with mild detergent, towel, warm blow dry.

**5. Temperature monitoring and control**. Maintain body temperature 38.0−39.0 °C

**6. IV crystalloids**. Aim for 1.5 × maintenance rates. Monitor packed cell volume/total plasma protein, electrolytes bid, check urine specific gravity when available.

**7. Ocular lubrication**. q4 h, eg, Lacrilube/Opticin.

**8. Bladder expression or urethral catheterisation**. q6−8 h (LMN bladder).

**9. Quiet, darkened environment**.

**10. Maintain sternal recumbency**, head slightly elevated, turn hind legs q6 h.

**11. Prevent self-grooming**. Apply E-collar once mobility improving.

*Source: Protocols, ARH, Strathfield South NSW Australia.

Permethrin exposure may result in severe clinical signs of toxicity in cats. Many cats require intensive supportive care and monitoring during treatment. Cats included in this study were not treated with methocarbamol. The most commonly used anticonvulsants included diazepam, phenobarbitone, midazolam, propofol and pentobarbitone. Complications during treatment occurred in 33% of cats and included hypothermia, electrolyte abnormalities, aspiration pneumonia, hypoproteinaemia, anaemia, apnoea, respiratory arrest, cardiorespiratory arrest, pleural effusion, urinary tract infection and corneal ulceration. Treatment of cases at our institution has altered recently with injectable methocarbamol now available in Australia (current ARH protocol − Table 4). Results of this study suggest that lack of availability of methocarbamol should not preclude treatment of feline permethrin toxicity.

Overall mortality rates may range from 2% to 37%. The majority of cats with permethrin toxicity are exposed to canine concentrated PSO products. Factors that may contribute to the misuse of permethrin products on cats may include: the availability of products in supermarkets where they can be purchased without veterinary advice, similar packaging of dissimilar products and failure of owners to read product packaging or failure to understand the consequences of misuse of such products. The APVMA reviewed small animal permethrin product labels in 2004−2006 and concluded that there were adequate label warnings.[4] Despite this, cases of feline permethrin toxicity continue to occur in Australia and the numbers of cases may be increasing.

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