



## Clinical effects and outcome of feline permethrin spot-on poisonings reported to the Veterinary Poisons Information Service (VPIS), London

Nicholas M Sutton BSc\*, Nicola Bates MSc, Alexander Campbell BSc

*Veterinary Poisons Information Service, Medical Toxicology Unit, Avonley Road, London SE14 5ER, United Kingdom*

Permethrin is a pyrethroid insecticide used in dermally applied spot-on flea treatments for dogs. Permethrin-based spot-on preparations are contraindicated in cats because of the high risk of toxicosis. The Veterinary Poisons Information Service (VPIS) is a 24-h access telephone service that provides veterinary professionals in the United Kingdom with information on the management of poisoned animals. In a review of 286 cases reported to the VPIS regarding inappropriate feline exposure to permethrin spot-on (PSO) preparations, 96.9% were symptomatic. Increased muscular activity (as evidenced by twitching, tremor, muscle fasciculations or convulsions) was common and occurred in 87.8% of cases. The duration of increased muscle activity was long, with convulsions lasting on average 38.9 h and tremors 32 h. Recovery typically occurred within 2 to 3 days but in some cases took 5 to 7 days. Death occurred in 10.5% of cases.

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Concentrated dermal spot-on treatments for the control of fleas and ticks are commonly used on household pets. A number of products are available over the counter, containing margosa oil (neem oil) or permethrin, or from veterinary surgeons, containing imidacloprid, fipronil or selamectin. Permethrin spot-on treatments are readily available from most major supermarkets and pet shops and are relatively less expensive than other products. Low cost, ease of purchase and a quick and simple means of application may account for the popularity of permethrin spot-on products.

Permethrin is generally considered to be of low toxicity to dogs (Richardson 1999). When used as directed by the manufacturer these spot-on products are considered safe and effective, with a relatively low risk of adverse reactions (Volmer et al 1998a). Cats, however, are particularly sensitive to permethrin, and consequently permethrin spot-on (PSO) products are restricted to use in dogs and other less

susceptible species (such as gerbils, guinea pigs, hamsters, mice and rats). However, despite package labelling giving cautionary advice, warnings are often ignored or unseen. Inappropriate use of PSOs on cats can cause severe toxicity, and frequently result in convulsions and fatalities (Meyer 1999, Bates 2000, Gray 2000, Martin and Campbell 2000). In addition to direct application, cats are also at risk from secondary exposure through contact with other pets treated with a PSO. Reports in the literature (Meyer 1999, Gray 2000, Martin and Campbell 2000, Gleadhill 2004, Merola and Dunayer 2006) and from unpublished data show that treated dogs can be a source of permethrin exposure in cats.

The Veterinary Poisons Information Service (VPIS) is a 24-h access telephone service that provides veterinary professionals in the United Kingdom with information on the management of poisoned animals. Cases of cats with severe clinical effects after inappropriate exposure to PSOs are frequently reported to the VPIS. Deaths from exposure are reported regularly. This paper aims to raise awareness of the extent of this problem, as well as highlight treatment options.

\*Corresponding author. Tel: +44-20-7635-9195; Fax: +44-20-7771-5309. E-mail: nick.sutton@gstt.nhs.uk

### **Permethrin spot-on treatments**

Permethrin (3-phenoxybenzyl-(1*R*,1*S*)-*cis,trans*-3-(2,2-dichloro vinyl)-2,2-dimethylcyclopropanecarboxylate) is a pyrethroid insecticide used in both agricultural and domestic products. Pyrethroids are synthetic derivatives of extracts from dried *Chrysanthemum cinerariaefolium* flowers.

PSO preparations are available in small volume containers, usually only 1 or 2 ml, but contain concentrated permethrin solutions. In the United Kingdom permethrin spot-on preparations for dogs are available in concentrations up to 74.4% (744 mg in 1 ml or 1488 mg in 2 ml).

### **Mode of action**

Permethrin is a neurotoxicant, acting on voltage-dependent sodium channels (Ray 1991). During normal repolarisation of nerves, sodium channels rapidly close. Permethrin-affected channels, however, are left open for prolonged periods of time. This extended channel opening causes an increased sodium current; consequently, depolarisation is prevented, leading to repetitive firing of the nerve.

In most mammalian species permethrin is metabolised to glucuronides and sulphates (Ray 1991). A feline deficiency of glucuronidase transferase may lead to prolonged detoxification, accounting for feline sensitivity to permethrin (Whittem 1995). While little information can be found on minimum toxic doses, dermal exposure in cats of 100 mg/kg of permethrin (equivalent to 1 ml of a 45% PSO in a 4.5 kg cat) has resulted in life-threatening effects (Hansen 2006).

### **Materials and methods**

For each VPIS poisons enquiry, an Information Officer completes a standard enquiry report form to record the history of each case. Follow-up questionnaires are sent out approximately 2 weeks after the enquiry to collect additional information such as: clinical effects that developed post-enquiry, treatments that were used and the clinical outcome. Information taken at both the time of enquiry and from follow-up questionnaires is then entered on to the VPIS database. The database holds details on all enquiries received, including: time and date of enquiry, details of the enquirer, animal species, the agent (poison) involved, clinical effects seen (type, severity, onset and duration), treatments used and outcome.

Data used for this study were collected from enquiries received between August 1988 and November 2006. Retrospective data regarding each case was collected from the series of permethrin cases held on the VPIS database. Analysis was performed only on cases with follow-up. Information for these cases was more complete, containing details of: the type of product involved, the clinical effects that developed and the outcome of the case.

In some enquiries received by the VPIS little information is known about what type of permethrin preparation is involved (ie, spot-on, flea collar, flea spray, agricultural pesticide, etc). At other times a spot-on is known to have been applied, but the chemical contents are unknown (ie, margosa oil, permethrin, fipronil, etc). In these instances data from these cases will be held on the VPIS database under 'agent not known' or 'insecticide not known'. Searching the VPIS database for 'permethrin' cases will, therefore, underestimate the number of true incidents that occurred. Consequently the database cannot be used to give an accurate account of the annual number of PSO cases. To try to establish an estimated annual incidence of PSO poisoning, information was collected prospectively over a 3-month period (1 September to 30 November 2006). In this period all permethrin exposures and enquiries regarding spot-on treatments were followed-up. Information from these cases was also included in the analysis of clinical signs, duration and outcome of permethrin toxicity in cats.

### **Results**

One thousand three hundred and six cases of permethrin exposure were extracted from the database from enquiries received between August 1988 and November 2006. Of these cases, 49.8% (650/1306) referred to enquiries regarding confirmed exposure to spot-on treatments, of which 80.9% (526/650) involved cats. The number of enquiries regarding feline exposure to other types of spot-on treatments during the same time period was much smaller, with 83 margosa oil (neem oil) and 141 fipronil enquiries.

Follow-up questionnaire information was available in 54.4% (286/526) of feline exposures to PSO treatments. These 286 cases with follow-up data were analysed for information on: the clinical signs reported, duration of effects and outcome of permethrin toxicity in cats.

Of the PSO cases where follow-up was available 96.9% (277/286) of cats developed signs of

toxicosis, while only 1% (3/286) remained asymptomatic. There was no information on the clinical course or outcome in 2.1% (6/286) of cases.

Clinical effects described in the follow-up questionnaire are reported in Table 1. Permethrin toxicity was characterised by increased muscular activity (as evidenced by twitching, tremor, muscle fasciculations or convulsions) which occurred in 87.8% (251/286) of cases.

Approximate reported recovery times indicate that convulsions last on average 38.9 h (range of 2 h to 5 days), tremors can persist for 32 h (range 2 h to 3 days) and overall recovery takes approximately 61.5 h (range of 3 h to 7 days).

Death occurred in 10.5% (30/286) of cases, 10 of which were euthanased. Reasons for euthanasia included respiratory failure (two cats), respiratory failure followed by cardiac arrest

unresponsive to resuscitation (one), convulsions not controlled by drug therapy (two) and unresponsiveness to treatment (one). In three cases death occurred before treatment could be started. In the remaining 21 cases no cause of death or reason for euthanasia was given. Time of death was only reported in two cases at 24 and 30 h post-exposure.

Analysing data from the 3-month study (1 September to 30 November 2006) to estimate the annual number of PSO cases showed that during this time the VPIS received 108 enquiries regarding permethrin exposure in cats, 82.4% (89/108) of which were confirmed exposure to a PSO. Twenty-nine follow-up questionnaires were returned and 13.8% (4/29) of these cats were reported to have died.

**Table 1.** Clinical signs reported in follow-up questionnaires in 286 cases of permethrin spot-on exposure in cats

| Clinical effect reported                | Frequency   |
|---|-------------|
| Convulsions                             | 125 (43.7%) |
| Twitching                               | 101 (35.3%) |
| Tremors                                 | 96 (33.6%)  |
| Hypersalivation                         | 65 (22.7%)  |
| Ataxia                                  | 63 (22.0%)  |
| Mydriasis                               | 41 (14.3%)  |
| Hyperaesthesia                          | 35 (12.2%)  |
| Hyperthermia                            | 35 (12.2%)  |
| Muscle fasciculations                   | 29 (10.1%)  |
| Tachycardia                             | 17 (5.9%)   |
| Lethargy                                | 11 (3.8%)   |
| Disorientation                          | 8 (2.8%)    |
| Vomiting                                | 7 (2.4%)    |
| Neurological effects<br>(not specified) | 6           |
| Hypothermia                             | 5           |
| Anxiety                                 | 4           |
| Cardiac arrhythmias                     | 4           |
| Collapse                                | 4           |
| Diarrhoea                               | 3           |
| Temporary blindness                     | 3           |
| Respiratory arrest                      | 3           |
| Head tilt                               | 2           |
| Alopecia                                | 1           |
| Lacrimation                             | 1           |
| Hallucinations                          | 1           |
| Paddling                                | 1           |
| Urinary retention                       | 1           |
| Cyanosis                                | 1           |
| Dyspnoea                                | 1           |
| Tachypnoea                              | 1           |
| Cardiac arrest                          | 1           |

## Discussion

Most cats exposed to permethrin develop toxic effects. In this study it was found that over 96% of cats were symptomatic. Clinical signs of feline permethrin toxicosis usually present within 3 h of exposure, but can be delayed until 72 h (Merola and Dunayer 2006). Toxicity typically manifests as stimulation of the central nervous system, including central neuropathies (excitability, twitching, tremor, hyperaesthesia and convulsions) and peripheral neuropathies (muscular weakness and fasciculations) (Whittem 1995). Other effects include hyperthermia (possibly as a result of increased muscular activity), respiratory distress (due to pulmonary muscle weakness), vomiting, diarrhoea, hypersalivation, anorexia and tachypnoea. More unusual effects include hallucinations, hypothermia, temporary blindness and cardiac effects. Effects of permethrin can be short-lived, but are more commonly prolonged. The average recovery time in the cases reported to the VPIS was 2 to 3 days, although one case took 7 days to fully recover. The reason for this long recovery period in this case is not apparent.

Clinical effects reported to the VPIS correspond with those reported in the literature. No animals appeared to exhibit long-term sequelae. Theoretical complications from permethrin toxicity include cerebral oedema, irreversible brain damage and myoglobinuria-induced neuropathy due to prolonged seizure activity (Richardson 1999).

Cats with dermal exposure to permethrin should be thoroughly washed with copious quantities of lukewarm water. The use of hot water should be avoided as it can increase dermal

perfusion and uptake of permethrin, resulting in more severe effects (Whittem 1995). Permethrin is insoluble in water and so a mild detergent, such as washing up liquid or shampoo should be used for washing (Whittem 1995). The detergent should then be thoroughly washed off to prevent secondary complications. Care should be taken to dry the animal well to reduce the risk of hypothermia, particularly in sedated animals (Volmer et al 1998a). A decrease in body temperature may exacerbate the effects of permethrin because of an inverse relationship between sodium influx and temperature (Whittem 1995). Cats can also be collared to prevent grooming and should be isolated from other animals to reduce the risk of secondary exposure.

Increased muscular activity is typical of permethrin toxicosis in cats. This study found that 87.8% of cats developed some form of twitching, tremor, muscle fasciculation or convulsion. Although most animals recovered with supportive care, many developed potentially life-threatening effects. Convulsions were the most frequently reported effect, occurring in 43.7% of cases, persisting for up to 5 days in a small number of cases.

Management of permethrin toxicity should be aggressive, with control of seizures being the main priority. Hydration should be maintained and supportive treatment should be initiated where appropriate. There is no specific antidote to permethrin and care is essentially supportive. Benzodiazepines such as diazepam (0.5–1 mg/kg body weight IV) could be used to control increased muscle activity (Valentine 1990). Care should be taken when giving benzodiazepines because of reports of paradoxical exacerbation of neurological signs in permethrin contaminated cats (Martin and Campbell 2000). In severe cases benzodiazepines may be ineffective at controlling seizures (Volmer et al 1998b) and alternatives will need to be employed. Barbiturates such as pentobarbital (3–15 mg/kg body weight by slow intravenous infusion) could be considered. However, pentobarbital is becoming less widely available in the UK and so phenobarbital could be used at a bolus of 2–5 mg/kg repeated up to two times at 20 min intervals (Plumb 2005). Infusions of phenobarbital can be used for the treatment of refractory convulsions at a suggested rate of 2–4 mg/kg/h, to a maximum of 24 mg/kg/24 h (Platt and Olby 2004). Methocarbamol, a centrally acting skeletal muscle relaxant, is an alternative to control increased muscular activity, and has been effective where

barbiturates have failed (Volmer et al 1998a, Richardson 1999, Hansen 2006). The dose to control seizures is 55–220 mg/kg orally, which can be repeated as required to a maximum dosage of 330 mg/kg/day (Volmer et al 1998a). Methocarbamol, has limited veterinary availability and experience in the UK, but may be available from hospital pharmacies. Tablets will need to be crushed and given via a gastric tube in sedated animals. A combination of diazepam and methocarbamol can be used for refractory convulsions (Volmer et al 1998a) or full anaesthesia may be required where alternative drug therapy has failed (Richardson 1999). In the literature isoflurane anaesthesia or propofol infusions have both been used with varying degrees of success (Volmer 2004, Hansen 2006).

Significant numbers of symptomatic cases result each year from feline exposures to PSOs. In many of these cases cats develop severe effects, with fatalities accounting for approximately one in 10 cases reported to the VPIS. Potentially life-threatening effects can occur at dermal exposures of less than 100 mg/kg (Hansen 2006). Exposure to a product containing 1488 mg of permethrin in 2 ml, equates to a dose of 330.7 mg/kg in a 4.5 kg cat. This is more than three times the potentially fatal amount quoted above. It is, therefore, unsurprising then that permethrin is the main toxicological cause of feline deaths reported to the VPIS. Due to incomplete data collection it is not accurately known how many permethrin cases are related to PSOs. However, extrapolation from the 3-month study would implicate that approximately 82% of permethrin enquiries concern spot-on preparations.

Data from the 3-month prospective study can be used to predict the annual number of permethrin spot-enquiries received by the VPIS. For this, seasonal variations need to be taken into consideration. Data show that calls received during the 3-month study period, should account for approximately 30.9% of the total annual number of permethrin enquiries (September 12.4%, October 10.2%, November 8.3%). Assuming that the percentages of spot-on cases remain constant in relation to other permethrin products (ie, flea sprays, powders, etc), then extrapolation of the 89 enquiries received over the 3 months, yields a predicted 288 cases per annum, of which approximately 30 (10.5%) might be fatal.

Although a predicted 288 cases per year are considerable, concerns arise that this is an underestimate of the total annual figure. Not all cases of permethrin spot-on toxicity are captured by

the VPIS, and currently there is no mandatory legal requirement to report fatal outcomes to any regulatory body in the UK. Cases may not be reported to the VPIS because the treating veterinarian may not require advice on treatment, or may not be a user of the VPIS. In some cases a PSO preparation may not be identified as the cause of an animal's illness, particularly where secondary exposure has occurred or the onset of effects are delayed. Also, owners may not report clinical effects or deaths to their veterinarian.

### Conclusions and recommendations

This study found that 96.9% of exposed cats developed clinical effects, 87.8% developed increased muscular activity and 10.5% of cases resulted in fatalities. These figures, along with a potentially underestimated prediction of 288 cases per annum, demonstrate that feline exposures to permethrin spot-on treatments are a common and dangerous problem.

Cases of feline poisoning from PSO products continue to occur despite warnings given on the product labels and in the literature. This implies that current cautionary labelling is not adequate or visible enough to prevent inappropriate use on cats. More needs to be done to raise awareness of pet owners to the life-threatening risks of permethrin exposure in cats. In addition to insufficient warnings some past exposures occurred as products had been packaged inappropriately, with pictorial representations of animals other than the intended target animal depicted on the container or packaging. Such practice undoubtedly led some owners to assume such products were safe for use in cats although intended for use on other animals.

Further study is required to determine more accurately the reasons and degree of morbidity and mortality in relation to feline PSO poisoning. This requires a combined effort on behalf of those in industry, regulatory bodies, the VPIS, veterinary practices and also owners themselves. Public awareness of this problem should be raised, while manufacturers need to review the impact and effectiveness of their warning labels.

The occurrence of permethrin poisoning comes at a high price to both cats and owners.

The cost of treating a severely poisoned cat can be expensive, especially if an animal is to be hospitalised for several days, while fatalities occur all too often. These accidents could be avoided with greater effort to improve feline safety through education and re-thinking of current safety warnings.

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