Permetherin toxicosis in cats

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A retrospective analysis of all adverse experience reports received by the Australian Pesticides and Veterinary Medicines Authority’s (APVMA’s) Adverse Experience Reporting Program for veterinary medicines since 1995, showed that permetherin toxicity in cats usually occurred after the owner applied a canine permetherin-containing product, typically a spot-on. Cats are also at risk from grooming or being in direct contact with recently treated dogs. This paper reviews permetherin toxicosis and its treatment in cats, incorporating information from the Australian and selected overseas veterinary pharmacovigilance programs.

Key words: permetherin toxicosis, cat, pharmacovigilance

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Flea control is a major problem for companion animal owners. There is a variety of flea control products and formulations on the Australian market, including spot-ons (for example, imidacloprid, imidacloprid/ivermectin, fipronil, fipronil/S-methoprene and permetherin), shampoos, rinses and sprays (pyrethrins and diazinon), injectable lufenuron, and oral products (lufenuron and cythioate). The environment, epidemiologically important in the control of flea infestations of animals, may also be treated with a variety of products (for example, diazinon).

There are currently 13 topical liquid and spot-on products containing permetherin that are registered for use in cats in Australia. These products contain low concentrations of permetherin (0.05 to 0.1%) and are suitable for cats if used according to label directions. In contrast, canine spot-on treatments, contain higher concentrations (45 to 65%) of permetherin and even exposure to very small amounts of these products, such as one drop from an ampoule or licking an empty permetherin product packet, may be lethal to some cats.a

This paper reviews feline permetherin toxicosis and presents the findings from the Australian Pesticides and Veterinary Medicines Authority’s (APVMA’s) Adverse Experience Reporting Program for veterinary medicines’ (AERP Vet) analysis of all adverse experience reports received since 1995 regarding permetherin products used on cats. Data from the pharmacovigilance programs in the United Kingdom and the United States is also considered.

Pyrethrums and related compounds

Pyrethrums is a natural plant product that is produced primarily from the flower heads of the Dalmatian Insect Flower (Chrysanthemum cinerariifolium) and the Persian or Painted daisy (Chrysanthemum coccineum). The first known record of pyrethrums being used as an insecticide was in the first century AD, during the Chou Dynasty of China. The plant was reputedly brought to Europe from China in medieval times.

Pyrethrums is a combination of six natural insecticidal esters called pyrethrins. The pyrethrins are contact poisons that act upon the nervous system. Their effectiveness against arthropods and their low mammalian toxicity has led to their widespread use as ectoparasiticides. The synthetic pyrethroids (for example, permetherin a third generation synthetic pyrethroid) have a broader spectrum of activity than the pyrethrins, with low but increased mammalian toxicity.

Nearly all pyrethrin and many pyrethroid products are formulated in combination with a synergist such as piperonyl butoxide (PBO) or n-octyl bicycloheptane dicarboximide, to enhance the effectiveness of the active ingredient. PBO, for example, inhibits microsomal oxidation and by itself has no parasiticidal properties, but when added to pyrethroid and pyrethrin insecticides, markedly increases their effectiveness. When mixed function oxidases are inhibited, the primary detoxification pathway for many pesticides is made non-functional, leading to higher systemic concentrations of the active constituent in the target insect.

Toxicodynamics

The mechanism of toxic action of the pyrethrins and pyrethroids has been categorised as two distinct groups, type I and type II, based upon the clinical signs of intoxication produced in rats. Type I pyrethroids, such as permetherin and resmethrin, bind to the sodium channels in the axonal membrane of nerves, thereby modulating the voltage-dependent gating kinetics. This causes a reversible prolongation of sodium conductance in the nerve axons and suppression of potassium conduction, leading to repetitive nerve discharges. Type II pyrethroids (cypermetherin and fenvarelate) cause a more prolonged opening of the sodium channels, leading ultimately to suppression of neurotransmission.
Pyrethroid modulation of sodium channels is dependent on temperature, with potency being augmented by lower temperatures, so hypothermic mammals may be at higher risk of increased toxicity.

Pyrethroids also increase the release of gamma-aminobutyric acid (GABA), a peripheral inhibitory neurotransmitter. Permethrin has been shown to inhibit GABA and glutamate receptor-channel complexes and voltage-activated Ca²⁺ channels, as well as calcium magnesium ATPase, which results in increased intracellular calcium levels and hence increased neurotransmitter release and postsynaptic depolarization. Various adenosine triphosphatases, including calcium ATPase and calcium magnesium ATPase in nervous tissues, are also inhibited by pyrethroids.

**Toxicokinetics**

Permethrin, a racemic mixture of cis and trans isomers, is rapidly absorbed from the gastrointestinal tract in all species examined, although the rate and extent of dermal absorption appears to be quite variable. In a study of dermal absorption of cis- and trans-permethrin isomers in rhesus monkeys and Sprague-Dawley rats, it was shown that rat skin absorbs significantly more permethrin than monkey skin. Permethrin may also be absorbed via inhalation of dust and fine spray mist.

After oral or dermal absorption, permethrin is metabolised by hepatic microsomal esterases and oxidases, followed by rapid hepatic hydroxylation and conjugation to either glucuronides or sulphates. This may provide one possible explanation as to why cats are more likely to develop permethrin toxicosis than dogs, as the feline liver is deficient in the glucuronide transferase enzyme. The trans isomer metabolism is dominated by hydrolysis (and excreted more rapidly) whereas the cis isomers are less easily hydrolysed and more toxic, so a slower rate of hydrolysis in cats compared to other species is a possibility. Research has shown that rapid hydrolysis of ester linkage in the digestive tract results in low oral toxicity.

Hydrolysis resistance is associated with low urinary (45 to 55%) and high faecal excretion of the cis isomers whereas trans isomers are primarily eliminated in the urine.

**Route of exposure**

Permethrin toxicity most commonly occurs when the owner inappropriately applies canine topical spot-on products to cats. This is supported by data from the Australian and United Kingdom veterinary pharmacovigilance programs, and from the ASPCA Animal Poison Control Centre (APCC) in the United States.

Information from the AERP Vet records showed that in 26 adverse reaction reports regarding permethrin exposures in cats, three-quarters (23) of the cats developed permethrin toxicity after the owner inappropriately applied the canine spot-on product. They were also affected by being in close contact with recently treated dogs (one-quarter of the cats). There was one incident of a cat developing clinical signs of permethrin toxicosis after licking an empty permethrin-containing packet.

In 2000, the Veterinary Medicines Directorate’s (VMD’s) Suspected Adverse Reaction Surveillance Scheme (SARSS) in the United Kingdom reported 18 incidents of suspected adverse reactions involving 27 cats that had been exposed to canine permethrin-spot-on products. Two of the 18 incidents (11%) involved close physical contact between treated dogs and cats.

**Clinical signs of toxicity**

According to the AERP Vet records, the clinical signs most commonly seen with permethrin toxicosis in cats were related to the central nervous system: seizures, muscle fasciculations, tremors, shaking and ataxia. Fifty-eight percent of all cases (15 cats) exhibited one or more signs of generalised tremors, muscle fasciculation (mild to severe) and shaking, and 38% (10 cats) had seizures. Twenty-three per cent of affected cats died. Other signs observed were emesis, ptosis, anorexia, collapse, diarrhoea, confusion, hyperaesthesia, lethargy and temporary blindness. This is consistent with the scientific literature, which reports that the clinical signs of toxicosis in cats are most likely attributable to the effects of the permethrins at the presynaptic nerve ending and are typical of nerve and muscle disorders.

There was no correlation between the amount of permethrin applied and the severity of the clinical signs, or breed or age of the cat. Interestingly, almost two-thirds of affected cats were aged 1 year or less, which could indicate an individual or age-related sensitivity to permethrin.

The onset of clinical signs was usually within a few hours of exposure with some being delayed for 48 hours. Clinical signs may be delayed up to 72 hours post exposure. The clinical signs resolved in either recovery or death within 24 to 72 hours, which is consistent with the published literature. Generally, early intervention improved the clinical outcome. According to APCC, VMD’s SARSS and Veterinary Poisons Information Service (VPIS) in London, generalised tremors, muscle fasciculations, hyperaesthesia, hyperthermia and seizures are the most common clinical signs seen with permethrin toxicosis. The VMD reported that 37% of affected cats died.

**Diagnosis**

Diagnosis of permethrin toxicosis is based primarily on the clinical history (access to permethrin), a thorough clinical examination to rule out other toxicological agents (strychnine, mycotoxins, lead and bromethalin rodenticides) and medical conditions (trauma, hypocalcaemia, hypoglycaemia and encephalitis), and the presenting (or developing) clinical signs. Haematological and biochemical values are usually normal, except for possible stress-related responses such as hyperglycaemia and neutrophilia.

Whilst pyrethroids are difficult to detect and confirm in blood or tissues, urine and plasma may be analysed for permethrin and its metabolites using liquid chromatography. Skin and hair samples, and necropsy samples of brain, fat, liver and cerebrospinal fluid, are also useful to confirm permethrin exposure. Although
the presence of permethrin and related compounds in body tissues confirms exposure, tissue concentrations do not correlate with the severity of clinical signs.

Treatment
Symptomatic treatment regimes instigated by veterinarians and reported to the AERP 
were based on control of the tremors and/or seizures, supportive care and decontamination. Intravenous catheters were placed whenever possible to facilitate the administration of drugs and fluids. Intravenous fluids were almost always used to correct the hydration level and help protect the kidney tubules from myoglobin breakdown products in actively seizuring and tremoring cats. Tremors or seizures were controlled with intravenous diazepam or barbiturate (pentobarbital and phenobarbital), intravenous methocarbamol, or gaseous anaesthesia. Sedation (heavy or light) was usually continued for 12 to 48 hours post-admittance. Inability to control seizure activity was the main reason for the death or euthanasia of cats exposed to permethrin.12,21–23

Most cats were washed in a shampoo or a mild hand dishwashing liquid with either local application (just the area the drug was applied to) or whole-body application. Body temperature was monitored for hyperthermia, which can occur as a result of muscle fasciculations or seizures, and hypothermia which may lead to a prolonged recovery due to sodium channel kinetics.21

Prognosis
The prognosis for tremoring or seizuring cats that are treated promptly and respond to treatment is good, although treatment may last 24 to 72 hours. The reader is referred to the published literature for details of recommended treatments.2,8,13,15,22 The majority of cats that received prompt and aggressive treatment, recovered within 48 to 72 hours and none had permanent sequelae. Cats that did not receive veterinary treatment and those more severely affected (for example had uncontrollable seizures), either died or were euthanased.

What is the APVMA doing?
The APVMA is the national agricultural and veterinary chemicals regulator and receives adverse experience reports from veterinarians, animal owners, farmers, product registrants and other chemical users within the general community. Reports received by the APVMA are assessed to determine whether the adverse experience is related to the use of, or exposure to, the product or not. Based on the assessment of adverse experience reports, certain risk mitigation strategies or corrective actions may be required. There are many factors that need to be, and are, considered when determining whether corrective action is required and if so, what corrective action is needed. The APVMA takes into account a broad range of issues and options when deciding what, if any, corrective action is required.24 These include the addition of label warning statements, changes to the formulation and education of product users through the media.

The APVMA extensively reviewed all the product labels for the registered permethrin products for dogs and cats in 2004 and again in 2006 following further receipt of adverse experience reports involving the off-label use of permethrin product in cats, and concluded that there were adequate label warnings on the products regarding off-label use. For example:

- Do not use on cats
- Not to be used for any purpose or in any manner contrary to this label unless authorised under appropriate legislation

A number of veterinary product registrants updated their product labels to be more descriptive in terms of not using permethrin products registered for use on dogs on cats (for example, a simple picture of a cat with a red line across it). The APVMA commends such action, and in light of it, decided not to take any regulatory action to improve the warning statements on the product labels. The importance of following the product label directions of permethrin products will be emphasised by the APVMA in various community and veterinary publications.

Summary
As many flea products are purchased outside the veterinary hospital, veterinary staff should educate their clients on the importance of reading and following the product label directions. The judicious use of any product is important but especially so for permethrin products as permethrin is a recognised cause of feline poisonings. Veterinarians and owners are encouraged to continue reporting adverse experiences involving permethrin products and cats to the APVMA, so that the situation can continue to be monitored and valuable information gathered. In this way, areas of concern can be identified and appropriate action taken as required.

References
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