Hyperactivity and alopecia associated with ingestion of valproic acid in a cat

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- Accidental ingestion of valproic acid by cats can result in severe alopecia and hyperactive behavior.
- It is unknown whether clinical signs in cats that ingest valproic acid are caused by an adverse reaction or toxicosis as a result of prolonged hepatic elimination of the drug.

A 1-year-old castrated male domestic shorthair cat weighing 10.1 lb (4.5 kg) was evaluated at the small animal clinic at the Texas Veterinary Medical Center because of alopecia of approximately 4 to 5 months' duration. Alopecia was most pronounced over the lateral aspect of the pelvic region, thighs, abdomen, and inside of the hind limbs, but some hair loss was also evident over the lateral aspect of the thorax and forelimbs as well. The referring veterinarian had treated the cat with steroids (dose and duration were unknown) and 1 injection of megesterol acetate[a] (dose unknown), with no apparent response. The owner reported no apparent health problems other than the alopecia. The cat had been castrated at 4 months of age, vaccinated as a kitten, and kept strictly indoors. The cat had been on several different commercially available kitten and cat foods, and was currently eating a commercially available adult cat food.[b]

Results of physical examination revealed the cat was alert and responsive, but extremely hyperactive (the cat was agitated and constantly pacing and grooming itself excessively in the examination room). The areas of alopecia had not changed appreciably from the original description given by the referring veterinarian. Lesions were bilateral and symmetrical; some hairs appeared broken in certain areas, whereas in other areas the hair was absent (**Fig 1**). The primary differential diagnoses for symmetrical alopecia in cats include ectoparasites (*Demodex cati*), dermatophytosis, hypersensitivities (flea bite hypersensitivity, atopy, and dietary hypersensitivity), and internal disease (eg, endocrinopathies, telogen defluxion, adverse drug reactions, and obsessive-compulsive disorders such as psychogenic alopecia).[1] Mild erythema was evident; however, papules, pustules, crusts, epidermal collarettes, or excoriations were not noticed. Unaffected areas of skin and coat appeared normal, and no external parasites were found. Results of multiple skin scrapings were negative for mites. Results of examination with a Wood's light revealed no fluorescence; however, a sample of hair was submitted for fungal culture. No growth was evident in the culture after a 10-day incubation period. Hairs suspended in saline (0.9% NaCl) solution were examined under a light microscope and appeared normal, with the exception of frayed ends suggestive of trauma induced by excessive grooming. Hairs that were intact contained hair bulbs that were in telogen; however, the overall percentage of these hairs was only 50%, which was normal for the season (ie, spring).[1] Cytologic examination of the skin surface of one area of alopecia was unremarkable; a skin biopsy was not performed. A CBC, serum biochemical analysis, and urinalysis were performed; all results were within reference ranges. An ACTH stimulation test was not performed, pending further evaluation for pruritic causes of alopecia. Because many of the hairs were broken, presumably because of excessive grooming, allergic skin disease (ie, flea bite hypersensitivity, atopy, or food allergy) was the initial diagnosis. Results of a flea antigen test were negative for immediate hypersensitivity to flea saliva; however, the owners chose not to pursue further skin testing for allergies and declined trying a food trial at this time. In an attempt to provide symptomatic relief for the apparent pruritus, treatment with methylprednisolone (4 mg of body weight, PO, q 12 h for 7 days, then q 24 h for 7 days, and q 48 h for 7 days) was initiated.

Figure 1—Photograph of a 1-year-old cat with bilaterally symmetric alopecia associated with ingestion of valproic acid. Hairs were broken, presumably because of excessive grooming; however, little or no new hair growth was evident. Lesions of the skin were not apparent.

After 2 weeks of treatment with steroids, there was no appreciable change in the amount of hyperactivity, pruritus, or excessive grooming behavior. In addition to continued treatment with methylprednisolone (4 mg, PO, q 48 h), a food trial was initiated, using a commercially available novel diet that consisted of venison and potato. The cat was reevaluated 6 weeks after the diet change was implemented; the pattern of hair loss and amount of pru-

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ritus or excessive grooming behavior had not changed, and the areas of alopecia appeared to be larger. The novel diet was discontinued after 8 weeks. At this time, differential diagnoses still included psychogenic alopecia and food allergy; atopy was considered less likely because there was no response to treatment with methylprednisolone. Although psychogenic alopecia was a possibility, the pattern of hair loss (ie, alopecia of the forelimbs, sternal area, flanks, thighs, and ventrum) was atypical for this condition. Further questioning regarding the cat's home environment revealed that the owner had a 4-year-old daughter with cerebral palsy who required medication 3 times daily with 500 mg of valproic acid[c]; the contents of 4 capsules (125 mg each) were mixed with the child's food for control of seizures. The cat often ate food that dropped onto the floor or onto the child's bib. To evaluate the possibility that the cat was consuming potentially substantial amounts of valproic acid, blood was drawn from the cat for measurement of serum valproic acid concentrations. Additionally, 1 of the child's bibs was obtained to determine whether substantial amounts of the drug were present in the child's drool and food that was dropped on the bib. The bib was soaked in water and the concentration of valproic acid was measured in the rinse solution. Serum valproic acid concentrations were measured in a laboratory by use of a polarized immunofluorescence assay; the lower limit of the assay is 0.7 µg/ml. The assay was not validated for use in cats; however, serum from a healthy cat was used as the negative control. The assay measures both protein-bound and free valproic acid, but not its inactive metabolite, valproate.

The cat had a serum valproic acid concentration of 3.4 µg/ml (therapeutic concentrations in humans are 50 to 100 µg/ml), which supported the assumption that the cat was ingesting valproic acid. To determine the approximate amount of valproic acid in the bib, it was soaked in 200 ml of sterile water, the rinse water effluent was collected, and the amount of valproic acid was determined. The bib measured 23 × 22 cm (surface area of 506 cm^2) and weighed 50.33 g. The total amount of valproic acid in the effluent was 720 µg, which corresponded to a concentration of 3.6 µg/ml of valproic acid in the rinse water from the bib. Alternatively, on the basis of the weight of the bib, the concentration of valproic acid was calculated to be 14.3 µg/g. Although the concentration of valproic acid was much higher in the food itself (500 mg/meal or approx 500 mg/cup of food), the cat had less direct access to the food than to the bib, which was worn more or less continuously by the child. To test the hypothesis that the cat's hyperactivity and alopecia developed as a result of ingestion of valproic acid, the owner was instructed to prevent the cat from having access to the child during feeding times and to change the bib after feeding the child. Because the cat was kept strictly indoors, and to avoid disrupting the household and the child's relationship with the cat, we only recommended that the cat be separated from the child during meals. Although this would not completely remove the cat's access to the source of valproic acid, the owner assured us that the majority of exposure to food was during meal times.

On physical examination 2 weeks later, the cat had less hyperactive behavior, and did not groom itself while in the examination room as it had in previous visits. Fuzzy curly hair was evident in the previously hairless areas. A blood sample was obtained from the cat at this time to determine serum valproic acid concentration, which was 2.6 µg/ml. The cat was rechecked again 1 month later, and serum valproic acid concentration was 1.5 µg/ml. At this time, the coat was clearly regrowing in all of the affected areas, and there were no new areas of alopecia or evidence of excessive grooming. Over the next 6 months, serum concentrations of valproic acid in the cat gradually decreased until the drug was undetectable. Eight months after the cat was removed from the source of valproic acid, its coat had completely regrown, although it was slightly lighter in color; grooming habits and general behavior had returned to normal (the cat was not considered to be hyperactive and was not constantly roaming).

Valproic acid is an anticonvulsant medication used for the control of generalized and partial seizures in adults and children, including absence, myoclonic, and tonic-clonic seizures.[2] In addition, valproic acid is increasingly being used for the treatment of bipolar and schizoaffective disorders, neuropathic pain, and prophylaxis of migraine.[2,3] Structurally, valproic acid is a simple branched chain carboxylic acid that was first approved for use in the United States in 1978.[2] There appear to be multiple mechanisms that contribute to the spectrum of action of valproic acid, including inhibition of repetitive firing by blockade of voltage-gated sodium channels, and, similar to phenytoin, valproic acid prolongs recovery of voltage-gated sodium channels.[2,4] In addition, valproic acid may affect neuronal calcium influx, but it does not appear to inhibit **γ–aminobutyric acid (GABA)**.[4] Recent evidence suggests that valproic acid may, in fact, increase GABA synthesis and potentiate GABAergic functions in some specific brain regions that control the generation of seizures.[3] Further, valproic acid appears to cause a reduction in the release of γ-hydroxybutyric acid and attenuates neuronal excitation induced by *N*-methyl-D-aspartate-type glutamate receptors.[3] This wide spectrum of anticonvulsant activity against different types of seizures, and the generally low toxicity, has made treatment with valproic acid in humans increasingly popular.

In humans, the pharmacologic profile of valproate is straightforward: the drug is rapidly absorbed when administered orally and is converted to valproic acid in the stomach; it is highly protein bound (90 to 95%), undergoes extensive hepatic metabolism and glucuronide conjugation, and has a serum half-life of 10 to 15 hours.[4,5] In dogs, it is slightly less protein bound (75 to 80%) and has a serum half-life of only 1.5 to 2.0 hours.[5,6] Because of the extremely short half-life and difficulty in achieving therapeutic serum concentrations, valproic acid has been used less commonly for control of seizures in dogs. Drugs that induce hepatic enzyme activity will increase the metabolism of valproic acid and further shorten its serum half-life; thus, the combination of valproic acid with phenobarbital is especially ineffective in dogs.[6] Half-life, protein binding, and metabolism of valproic acid in cats is not known.

Toxicosis associated with valproic acid is uncommon in humans, but when it does develop, the adverse

effects can be quite serious and include teratogenicity and severe hepatotoxicity.[2,3] Other reported toxicoses in humans include red cell aplasia, thrombocytopenia, sedation, psychosis, dementia, pancreatitis, appetite stimulation, and dermatologic effects (including alopecia, generalized pruritus, erythema multiforme, and hair changes).[5,7-10] Although the mechanisms for hair loss and pruritus in humans are unknown, increased numbers of hairs in telogen has been reported.[3] Although most of these adverse effects are uncommon, when they do develop in humans, they may persist long after treatment is discontinued. The owners would not consent to a skin biopsy for this cat, so a better description of the dermatohistologic characteristics could not be obtained. In dogs, treatment with valproic acid may also cause gastrointestinal tract upset, increases in hepatic enzyme activities and, like other anticonvulsants, sedation or drowsiness is often observed.[6] Although there is some clinical and pharmacologic data regarding use of valproic acid in dogs, to our knowledge, there is no information regarding the efficacy, toxic effects, or pharmacologic profile of this drug in cats. The extensive hepatic metabolism and glucuronide conjugation that are induced by valproic acid may increase the toxic potential of this drug when used in cats, which as a species are deficient in several hepatic enzymes necessary for drug metabolism, including glucuronidase.[10]

Because multiple samples were obtained to monitor the decrease in valproic acid concentrations over time, we used these values to calculate the serum half-life of valproic acid in this cat. On the basis of the first 3 time points, an elimination rate of 0.019^{-1} days and a half-life of 36.1 days were calculated. However, these numbers should be regarded with caution, because the owner could not assure us that the cat had no further access to the child's food or bib, especially during the first 2 to 3 weeks after the initial valproic acid concentration was determined. Thus, it is not possible to determine whether cats truly have a prolonged elimination rate and half-life for valproic acid, compared with humans. In fact, because the concentrations of valproic acid found in the cat of this report were extremely low (compared with the therapeutic range in humans), it is likely that the hyperactivity and alopecia that developed were the result of an adverse drug reaction rather than toxicosis or lack of ability to metabolize the drug. Alternatively, if this cat was constantly reexposed to valproic acid, and the true half-life of this drug was actually closer to that reported in humans, then the peak serum concentrations in this cat could have been much higher following exposure to the child's food, indicating a possible toxicosis. However, because serum concentrations of valproic acid were consistently low, even during the times when clinical signs were most obvious, toxicosis would appear to be less likely. Further work is necessary to determine the true pharmacologic profile of valproic acid in cats.

This report emphasizes the importance of obtaining a careful and complete history from the owner regarding an animal and its environment; in the cat of this report, exposure to valproic acid was accidental and considered inconsequential by the owner. The nature of the household situation gave additional credibility to the possibility of psychogenic alopecia as the cause of alopecia in this cat, but the hyperactive behavior and excessive grooming did not change until access to the drug was removed. Finally, although further work must be performed to accurately represent the pharmacokinetic profile of valproic acid in cats, it appears that exposure to small amounts of valproic acid may result in adverse effects.

[a]Ovaban, Par Pharmaceuticals, Spring Valley, NY.
[b]Eukanuba Chicken and Rice Adult Formula, Iams Co, Dayton, Ohio.
[c]Depakote Sprinkle Capsules, Abbott Labs, Chicago, Ill.

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