Special Report

Adverse drug event reports at the United States Food and Drug Administration Center for Veterinary Medicine

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The FDA Center for Veterinary Medicine (CVM) monitors reports of adverse drug events (ADEs [form 1932 and 1932A reports]) for drugs given to animals, medicated feeds, and veterinary devices. An ADE is an undesired effect or lack of a desired effect for claimed indications. Previously, colleagues described details of the ADE evaluation and reporting process.1,2 All data discussed in this report are from the FDA–CVM database and hotline log. The database uses a 6-part scoring system to evaluate drug reactions and product defects that are reported directly from manufacturers on FDA form 1932, from pet owners on form 1932A, or via hotline calls to 1-888-FDA-VETS. It is a modified Kramer scoring system with components that include previous experience with the drug (the label safety and adverse effects and the existing database of postmarketing form 1932 reports); alternative etiologic candidates; timing of the event; overdose, if it exists; dechallenge (effects of drug withdrawal); and rechallenge (effects of drug readministration).

Accomplishments during the last decade include Web site posting of ADEs so that the general public and veterinary practitioners may readily avail themselves of growing tables of information for each product in the CVM database; a growing awareness by practitioners and the public of the value of reporting ADEs, evidenced by a growing number of ADE reports each year; and opening communication channels for ADE reporting among regulatory authorities of the USDA, Environmental Protection Act, and FDA–CVM.

The purpose of this report was to increase the awareness of practicing veterinarians regarding the ADE reporting system in the United States and to illustrate why reporting ADEs is ultimately helpful in updating labeled safety information.

ADE Reports

The 4,000 ADEs received in 1997 increased to approximately 24,000 in 2001 and similar numbers in 2002 and 2003 (Figure 1). The use of a database has allowed more rapid entry and retrieval of additional information, such as medical history; alternative etiologies, concomitant drug exposure, and extralabel usage. The ADE Review Team has been expanded from the 4 part-time veterinary practitioners hired in 1998 to 7 part-time veterinary practitioners as of 2004. This has resulted in more timely processing of ADE reports.

Typically, new-animal-drug manufacturers invest several years developing protocols and submitting data as evidence of safety and efficacy in support of a New Animal Drug Application. This evidence is reviewed by the CVM Office of New Animal Drug Evaluation to determine whether or not a drug is safe and effective for its intended use. Safe in this context means safe for the target animal, the humans using the new animal drug or consuming edible tissues from the treated animals, and the environment. The CVM communicates the safety, efficacy, and conditions of use determined through their evaluation in the product labeling. After approval, the CVM continues to monitor the use of new animal drugs to ensure that they remain safe and effective when used in the general population. The monitoring of drug risk information is an indefinite process.
process over the life of a marketed drug product. Subsequent to the 1998 publication of the Adverse Drug Experience Reporting Program, several examples of ADEs have highlighted the value of ongoing rigorous surveillance and reporting.

**Blindness associated with high doses of enrofloxacin in cats**—Reversible vision loss correlated with the administration of quinolone antimicrobials was reported nearly a decade ago in humans receiving ciprofloxacin. Similar complaints have been documented in veterinary medicine after the administration of fluoroquinolones in companion animals. Review of the database revealed 1 complaint in 1992, 1 in 1995, and 2 in 1997. In 1998, the CVM received 14 complaints of blindness in cats after administration of enrofloxacin. By April of 2000, 52 episodes of complete or partial blindness had been reported to CVM from industry, owners via the ADE hotline, and veterinarians, including general practitioners and diplomates of the American College of Veterinary Ophthalmologists. As the complaints increased, the CVM worked with the industry to identify the potential problems and minimize future occurrences.

Most affected cats had been treated at the approved label dosage. At the time, it was a flexible label dosage of 5 to 20 mg/kg/d (2.3 to 9.1 mg/lb/d). This label dosage had been changed from 2.5 mg/kg (1.1 mg/lb) every 12 hours in July 1997, the year before a cluster of complaints. This label change also included cats as an approved species for oral administration of enrofloxacin.

Among all cats reported with blindness associated with administration of enrofloxacin (n = 141 through 2002), 99 received only oral administration of enrofloxacin. Nineteen of 61 cats reported prior to July 2000 received an unknown dosage and were not included in the analysis. Examination of the total daily dosage for the remaining 42 of those reported prior to July 2000 revealed that only 2 of the blind cats received ≤ 5 mg/kg/d. Thirty-seven of the 42 received 5.1 to 20 mg/kg/d. The remaining 5 received variable off-label doses or > 20 mg/kg/d overdoses.

In July 2000, the manufacturer of the product sent a letter to veterinarians advising that there might be a problem with visual disturbances (blindness, partial blindness, and retinal damage) at the upper range of the label dosage and recommended that cats receive no more than 5 mg/kg/d until studies could be completed. After further investigation, the CVM required the manufacturer to send a notice to veterinary practitioners regarding the problem. This was sent in March 2001 in the form of a Dear Doctor letter that confirmed the association between administration of high-dosage enrofloxacin and visual disturbances and emphasized the new label dosage of ≤ 5 mg/kg/d.

Review of the ADEs for enrofloxacin received from April 30, 2001, to March 22, 2002, revealed 39 complaints of vision abnormalities in cats, primarily mydriasis and blindness with retinal lesions. Of these, 18 cats received only tablets; however, they received > 5 mg/kg/d (range, 5.6 to 34 mg/kg/d [2.5 to 15.5 mg/lb/d]). Five cats received only injections, and 7 received both tablets and injections. The reason for giving higher dosages was not always provided in the reports. In several instances, the correct dosage was prescribed, but the owners mistakenly gave the tablets twice per day, effectively doubling the dosage. In a few other instances, the veterinarian did not seem aware of the change in the label dosage.

Only 9 cats had vision abnormalities at orally administered dosages ≤ 5 mg/kg/d. Of these 9 cats, abnormalities in 6 had other possible etiologies (eg, anesthesia, West Nile virus infection, hypertension with retinal detachment, suspected toxoplasmosis, or diabetes mellitus). Ages ranged from 1.5 to 16.5 years. Of the 3 cats with no other identified etiology for their abnormality, 2 that received 5 mg/kg/d regained their vision within days after withdrawal of the enrofloxacin. One of these cats was 4 years old and had a urinary tract infection, and the other was 14 years old and possibly had otitis media. Laboratory values were not supplied. The third cat, a 12-year-old cat that had received 3 mg/kg/d (1.4 mg/lb/d), was not completely blind, but vision still remained poor 1 month after withdrawal of enrofloxacin. Laboratory values were within reference ranges.

Pharmacologic experts have postulated that the relatively open blood-brain barrier in cats, combined with the lipophilic properties of enrofloxacin, predisposes cats to accumulating high concentrations of the drug in the CNS. Additionally, a retrospective clinical study was undertaken to examine retinal degeneration in 33 cats at the University of Florida. The results indicated that some cats may regain vision but that there was often diffuse loss of the outer nuclear and photoreceptor layers and hypertrophy and proliferation of the retinal pigment epithelium. Authors emphasized the need to adhere to the revised dosage recommendation for cats.

In a recent article, possible risk factors that predispose cats to enrofloxacin-induced retinal degeneration are discussed. They include the possibility of altered drug disposition in urinary tract infections with concomitant renal impairment, even in young cats. The authors suggest that this represents a dose- and concentration-dependent ADE, rather than an idiosyncratic reaction. They conclude that greater attention should be paid to dosage in geriatric cats or those with renal or liver impairment. Since 1997, marbifloxacin and orbifloxin have been made available. Sporadic reports of blindness have been received by the CVM (11 for animals that received marbifloxacin and 16 for animals that received orbifloxin), but these were not attributed to the drugs.

**Overdoses of moxidectin in horses associated with failure of a syringe-locking device**—A portion of ADEs recorded for any single product relate to product defects. Such events are considered adverse typically because of sequelae related to manufacturing, packing, or dispensing. Moxidectin-related overdoses comprised most such ADEs and were related to slippage of the syringe locking mechanism during administration of the product resulting in accidental overdoses. Since marketing of the product began, 1,027 reports of ADEs associated with the use of moxidectin in horses have been received; 252 of all reports contained a complaint
about the locking mechanism on the dosing syringe. These events resulted in signs associated with accidental overdose that were primarily neurologic (ataxia, trembling, seizures, and incoordination). The CVM product managers worked with industry to produce an improved syringe lock, resulting in much reduced numbers of overdoses in horses. Cases decreased from 65 in the period January 1, 1998 to January 1, 2000, to 13 in the period January 1, 2000 to January 1, 2001, to 2 in 2001 and none in 2002.

Keratoconjunctivitis sicca associated with use of etodolac in dogs—Keratoconjunctivitis sicca in association with administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has been reported in humans and dogs. Complaints of keratoconjunctivitis sicca comprised 78 of 1,169 total etodolac-associated ADE reports during a 28-month period from 1999 to 2001. Mean age of dogs was 10.2 years (age was not reported for 13 dogs). Range of onset times after first drug administration was wide, spanning 6 days to 18 months; most incidents occurred between 3 months and 1 year after first administration.

Adverse drug events associated with keratoconjunctivitis sicca were not strongly associated with any certain breed. The database only contains 1 Bulldog; 1 Pug; 1 Lhasa Apso; and no Shih Tzus, Cocker Spaniels, or West Highland White Terriers. In contrast, the database contains 12 German Shepherd Dogs, 13 Golden Retrievers, and 14 Labrador Retrievers. This distribution appears to correlate with breeds in which NSAIDs are likely to be used, rather than true breed-associated ADEs.

Systemic problems associated with NSAID-associated ADEs in dogs—Adverse drug events associated with carprofen comprise the largest single database within the CVM ADE files because of the drug's widespread use and long time in market. Adverse events associated with administration of etodolac, deracoxib, tapoxinil, and meloxicam have also been described on our Web site. The CVM receives most complaints regarding NSAID-associated ADEs via industry submissions; however, a number of hotline calls are also received from owners and practitioners. Although small compared with the overall numbers of dogs for which NSAIDs are prescribed, the number of ADE reports in the data bank associated with these drugs exceeds other companion animal drugs by a large number.

Since approval, the manufacturers of NSAIDs have made a number of requested changes to try to mitigate the seriousness of outcomes for dogs that have ADEs. Information about how practitioners prescribe and dispense NSAIDs has revealed problems. Review of our hotline calls indicates that in the owner's mind, the most common problem associated with NSAID-associated ADEs is failure of veterinarians to follow recommended label precautions. A review of hotline calls received in 2001 and 2002 revealed certain specific complaints related to NSAIDs, including 23% of owners who stated that their veterinarian never discussed any adverse effects of the medication, 22% who stated that their veterinarian did not give them the client information sheet provided by the pharmaceutical company with each vial of medication, 14% who stated that the veterinarian dispensed the NSAID in containers that were not the original and intended packaging, and 4% who stated that preadministration blood analyses were not performed.

The CVM has, from time to time, used a Dear Doctor letter to bring important safety and efficacy information to the attention of practitioners. Regulatory guidelines exist to ensure that practitioners do not confuse such literature with promotional material. The CVM, through the Code of Federal Regulations (21 CFR 200.5), specifically requires that the mailings be distinctive. Practitioners should be alert to the appearance of Dear Doctor letters in

Dear Doctor Letters

The CVM has processed 17,442 carprofen-associated ADEs (12,511 caplets and 4,931 chewable preparations) during 90 months, 1,381 etodolac-associated ADEs during 60 months, 390 deracoxib-associated ADEs during 8 months, and 285 meloxicam-associated reports during 12 months. Despite much anecdotal information about ADEs involving NSAIDs, published retrospective studies in dogs with NSAID-associated ADEs are few. The CVM's ADE data are similar to the relatively scant literature on carprofen-associated ADEs and to much of the putative evidence regarding general ADEs associated with NSAIDs, which primarily involve the gastrointestinal, hepatic, hematopoietic, nervous, integumentary, and urinary systems.

Hepatocellular, renal, hematologic, and gastric or duodenal mucosal damage was often detected along with clinical signs related to the stomach, biliary system, and spleen. Judicious use according to label recommendations with fully informed pet owners often resulted in favorable outcomes for dogs because early detection of problems resulted in timely treatment.

Labrador Retrievers and Golden Retrievers are the most commonly affected breeds when NSAIDs are used; German Shepherd Dogs and Rottweilers are next in prevalence of ADEs. Again, this relationship bears similarity to canine breed, breed use, and breed-by-weight proportions in the United States and may not indicate that these breeds are more prone to NSAID toxicosis; the proportions of affected breeds may be attributable to the fact that more Labrador Retrievers and other retrievers that weigh 34 to 45 kg (75 to 99 lb) are owned in the United States, compared with other breeds, and more dogs in this weight range are likely to develop arthritis, play sports, and have lifestyles that make them candidates for drugs used to treat arthritis, compared with other breeds.

Time of onset of NSAID-associated ADEs was most commonly from days 14 to 30 after first administration, although the range of onset was from 3 to 90 days. Dogs > 3 years old were more commonly affected in all NSAID groups. Affected dogs were typically from 10 to 15 years of age, followed by dogs 6 to 10 years of age.
the future. Manufacturers and distributors of drugs must follow formats prescribed by regulation for the Dear Doctor letters. Despite this requirement by the FDA, we commonly understand from telephone calls that veterinarians do not recall seeing this information. Although the response to such material posted in the public domain on the CVM Web site is favorable, this response is largely from consumers who have already experienced the loss of a pet from an NSAID reaction.

Future Improvements

The CVM is presently working to develop guidelines for electronic submissions of ADEs by industry. Scanning of paper submissions and translation to permit portable document format searches are in the testing stage. Web-based reporting is another possibility. All improvements are contingent on the acquisition of funding.

In creating these guidelines and formats, the CVM is using procedures developed through the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) process and helping to forge communications with professionals around the world. The VICH is a trilateral (European Union-Japan-United States) program aimed at harmonizing technical requirements for veterinary product registration.16 Presently, the CVM hopes to work more closely with industry and other offices within the FDA to foster cooperation between those gathering information at the pharmaceutical companies and those managing product ADE reports within the CVM.

References


