

Incidence of adverse events in ferrets vaccinated with distemper or rabies vaccine: 143 cases (1995–2001)

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Objective—To determine the incidence of adverse events in ferrets vaccinated with a modified-live avian cell culture canine distemper virus vaccine licensed for use in ferrets, an inactivated rabies vaccine licensed for use in ferrets, or both.

Design—Retrospective study.

Animals—143 ferrets.

Procedure—Medical records were reviewed to identify ferrets that had an adverse event after vaccination.

Results—Adverse events developed within 25 minutes after vaccination in 13 ferrets. One ferret developed an adverse event after receiving a distemper and a rabies vaccine simultaneously and developed a second adverse event the following year after receiving the rabies vaccine alone. Therefore, a total of 14 adverse events were identified. All adverse events were an anaphylactic reaction characterized by generalized hyperemia, hypersalivation, and vomiting. Ten of the 14 anaphylactic reactions occurred after ferrets received both vaccines, 3 occurred after ferrets received the distemper vaccine alone, and 1 occurred after a ferret received the rabies vaccine alone. Incidences of adverse events after administration of both vaccines, the distemper vaccine alone, and the rabies vaccine alone were 5.6, 5.9, and 5.6%, respectively. Ferrets that had an anaphylactic reaction were significantly older at the time of vaccination than were ferrets that did not.

Conclusions and Clinical Relevance—Results suggest that there may be a high incidence of anaphylactic reactions after vaccination of domestic ferrets. Ferrets should be observed for at least 25 minutes after vaccination, and veterinarians who vaccinate ferrets should be prepared to treat anaphylactic reactions. (*J Am Vet Med Assoc* 2003;223:663–665)

Domestic ferrets (*Mustela putorius furo*) are susceptible to infection with **canine distemper virus (CDV)**, and because the mortality rate in ferrets infected with CDV is nearly 100%, vaccination is strongly recommended.¹ Since 1938, a variety of CDV vaccines have been used in ferrets, including modified-live virus vaccines attenuated in ferret,² canine,^{2,3} avian,^{2,8} and simian^{5,9} cell culture, as well as, most recently, recombinant

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canary pox-vectored vaccines.^{10,11} Inactivated CDV vaccines are not recommended because of variable efficacy.⁴

Vaccine-induced distemper and death have occurred in domestic ferrets given modified-live canine cell culture multivalent vaccines licensed for use in domestic dogs.^{1,4} Avian cell culture CDV vaccines apparently are less likely to revert to virulence in ferrets,^{6,8} and in the early 1990s, a modified-live avian cell culture CDV vaccine^a and an inactivated rabies vaccine^b were licensed for use in ferrets. Since then, there have been anecdotal reports of anaphylactic reactions after vaccination with this distemper vaccine.^{4,5} However, there have not been any published studies of the incidence of adverse effects in a large group of ferrets. The purpose of the study reported here, therefore, was to determine the incidence of adverse events in ferrets vaccinated with a modified-live avian cell culture CDV vaccine, an inactivated rabies vaccine, or both. The USDA Center for Biologics defines an adverse event as "any side effect, injury, toxicity, or sensitivity reaction (or failure to perform as expected) associated with use of an animal drug, whether or not determined to be attributable to the drug."¹²

Criteria for Selection of Cases

Medical records of all ferrets vaccinated at the University of Georgia Veterinary Medical Teaching Hospital between July 1, 1995 and February 1, 2001 were reviewed. Ferrets vaccinated with a modified-live avian cell culture CDV vaccine licensed for use in ferrets,^a an inactivated rabies vaccine licensed for use in ferrets,^b or both were eligible for inclusion in the study.

Procedures

Information obtained from the medical records included type, expiration date, and serial numbers of vaccines administered; date of vaccination; age at the time of vaccination; sex; coat color; clinical features and time of onset of any adverse event; treatments administered for any adverse event; and outcome. Adverse events associated with vaccination included local or generalized hyperemia, vomiting, diarrhea, dyspnea, and swelling at the injection site.

Age and sex distributions of ferrets that had an adverse event were compared with age and sex distributions of ferrets that did not have an adverse event with nonparametric ANOVA and the χ^2 test, respectively. Values of $P < 0.05$ were considered significant.

Results

Ferrets—A total of 143 ferrets met the criteria for inclusion in the study. One hundred thirty ferrets did

not have any adverse events following vaccination. Of these, 69 (53%) were male and 55 (42%) were female (sex of 6 [5%] was not recorded). All 130 had 2 dot tattoos in their right ear signifying that they had been neutered (castrated or spayed) and descended. Age at the time of vaccination ranged from 2 months to 6.25 years (median, 1.4 years). Most were sable (Table 1).

The remaining 13 ferrets had adverse events following vaccination. This included 4 castrated males and 9 spayed females. Age at the time of vaccination ranged from 1.25 to 5 years (median, 3.25 years), and 11 of the 13 were sable. One ferret had an adverse event after receiving the distemper and rabies vaccines simultaneously and had another adverse event after receiving only the rabies vaccine the following year. Thus, a total of 14 adverse events were recorded.

Vaccines administered—A total of 427 vaccine doses were administered to a total of 143 ferrets during 248 visits to the veterinary teaching hospital. All vaccines were given SC in accordance with the manufacturers' directions. The CDV vaccine was consistently given on the left side of the scapular region, and the rabies vaccine was consistently given on the right side. If both vaccines were administered, injection sites were at least 2 cm apart. No premedications were administered to any of the ferrets. Ferrets were monitored in the hospital for at least 25 minutes after vaccine administration. No particular vaccine serial number was associated with more adverse events than another. Forty-four of the 130 (34%) ferrets that did not have any adverse events had a history of previous vaccination with a CDV or rabies vaccine or both, including 1 ferret that had been vaccinated 6 times previously and 5 ferrets that had been vaccinated 5 times previously. Prevalence of previous vaccination was not significantly ($P = 0.15$) different between ferrets that had an adverse event (4/13) and those that did not (67/130).

Table 1—Clinical characteristics of 143 ferrets examined at a veterinary medical teaching hospital between 1995 and 2001 for vaccination against distemper, rabies, or both and that did ($n = 13$) or did not (130) develop an anaphylactic reaction after vaccination

Factor Category	No. of ferrets		
	Anaphylaxis	No anaphylaxis	Incidence of anaphylaxis (%)
Vaccines administered*			
Distemper and rabies	10	169	5.6
Distemper alone	3	48	5.9
Rabies alone	1	17	5.6
Sex			
Castrated male	4	69	5.8
Spayed female	9	55	16.4
Not recorded	0	6	0
Coat color			
Sable	11	104	11.5
Silver	1	10	10
Albino	0	10	0
Cinnamon	1	0	100
Not recorded	0	6	0

*One ferret developed an anaphylactic reaction after receiving a distemper and a rabies vaccine simultaneously and developed a second anaphylactic reaction the following year after receiving the rabies vaccine alone. Several ferrets that did not develop anaphylactic reactions were vaccinated multiple times.

Adverse events—All 14 adverse events consisted of an anaphylactic reaction 5 to 25 minutes after vaccine administration. Clinical signs included generalized hyperemia (most visible on the nose, mucous membranes, and footpads), hypersalivation, and vomiting. Five ferrets developed dyspnea, and 2 of the 5 were cyanotic. Five ferrets had diarrhea, and 2 of these had hematochezia. Ten adverse events occurred after administration of both vaccines, 3 occurred after administration of the distemper vaccine alone, and 1 occurred after administration of the rabies vaccine alone.

The relative risk (2.6; 95% confidence interval, 0.83 to 7.94) of an adverse event in female ferrets was not significantly ($P = 0.09$) different from the risk in males. Ferrets that had adverse events were significantly ($P < 0.003$) older than ferrets that did not. Incidences of adverse events after administration of both vaccines, the CDV vaccine alone, and the rabies vaccine alone were 5.6, 5.9, and 5.6%, respectively (Table 1). These values were not significantly ($P < 0.001$) different. Four of the 13 ferrets that had an adverse event were subsequently given the rabies vaccine alone, and only 1 had another adverse event.

Ferrets were determined to be healthy before 10 of the 14 vaccinations that resulted in adverse events. The remaining 4 adverse events developed in ferrets that had weak-positive heartworm antigen test^c results at the time of vaccination ($n = 1$), were suspected to have an adrenal tumor (1), and were recovering from a brief period of anesthesia with isoflurane for concurrent diagnostic testing (2). One of the 2 ferrets recovering from isoflurane anesthesia at the time of vaccination had undergone adrenalectomy 10 days prior to vaccination and had received a dose of prednisone (0.35 mg, PO) 24 hours prior to vaccination.

In all ferrets, anaphylaxis was treated with epinephrine (0.1 mL of a 1:1,000 solution, SC), diphenhydramine (1 mg/kg [0.45 mg/lb], SC, or 0.5 mg/kg [0.23 mg/lb], PO), and dexamethasone (2 mg/kg [0.9 mg/lb], SC). Supplemental oxygen was administered to ferrets with dyspnea. One ferret was given a second dose of epinephrine 4 hours after the initial treatment because of a recurrence of clinical signs (vomiting). All ferrets survived.

Discussion

Development of an anaphylactic reaction within 25 minutes of vaccine administration strongly suggests that vaccination was the cause of the adverse events in the ferrets described in the present report. However, the specific component of these vaccines that caused anaphylaxis remains unknown. In particular, most ferrets that had an anaphylactic reaction received both vaccines simultaneously, making it impossible to implicate 1 or the other vaccine. Even in the 1 ferret that had a reaction after receiving both vaccines and subsequently had a reaction after receiving only the rabies vaccine, it can only be said that the rabies vaccine was either partially or entirely the cause of the initial adverse event.

Although 9 of the 13 ferrets that had an adverse event did not have any history of previous vaccination,

they were probably not antigenically naïve, since most pet ferrets originate from a single commercial breeding facility that gives an avian cell culture CDV vaccine^d developed for mink to all ferrets prior to shipment.^e The percentage of ferrets with a history of previous vaccination was not significantly different between ferrets that had an adverse event and ferrets that did not.

Sex and coat color were not associated with whether ferrets had an adverse event in the present study. The median age of ferrets with an adverse event was significantly greater than the median age of ferrets that did not, probably because of repeated vaccination of ferrets < 14 weeks old (before maternal immunity had waned) and, possibly, the fact that older ferrets were exposed to more antigen.

Incidences of adverse events after administration of both vaccines, the CDV vaccine alone, and the rabies vaccine alone were not significantly different from each other. The US Pharmacopeia Veterinary Practitioner Reporting Program received reports of 83 adverse events, all anaphylactic reactions, associated with vaccine administration in ferrets between 1995 and 1999.¹³ Fifty-four of these events were in ferrets given only a CDV vaccine, 9 were in ferrets given only a rabies vaccine, and 20 were in ferrets given both vaccines. Epinephrine and diphenhydramine usually reversed the clinical signs, although 8 of these 83 ferrets died.¹³ Between September 1998 and August 2001, the USDA Center for Veterinary Biologics received reports on 210 ferrets that had anaphylactic reactions after receiving vaccines; 154 had received a CDV vaccine, and 56 had received a rabies vaccine; however, it is not known how many ferrets received both vaccines simultaneously.^f In addition, it is not known how many of the reports received by the Center for Veterinary Biologics were duplicates of reports received by the Veterinary Practitioner Reporting Program. More importantly, it seems likely that many adverse events are not reported to either agency. Adverse events should be reported to the USDA Center for Biologics by calling 1-800-752-6255 or by filing electronically through their Web site (<http://www.aphis.usda.gov/vs/cvb>).¹² As a courtesy, the manufacturer should be called as well. The USDA is currently developing regulations making it mandatory for vaccine manufacturers to report any and all adverse events to the USDA, similar to a system currently used in Canada.¹³

A tolerable limit for the incidence of adverse events secondary to vaccination has not been established in veterinary medicine, and any such limit would depend on the severity and prevalence of the disease for which vaccines are administered. Nevertheless, the incidence of anaphylactic reactions in the ferrets described in the present report is clinically important. In the United States, veterinarians may be held liable for adverse outcomes following usage of a licensed vaccine, even if the vaccine is administered in accordance with the manufacturer's label direction. To prevent liability, veterinarians should be able to

demonstrate that they provided an acceptable standard of care and documentation that clients provided informed consent prior to vaccination.¹⁴

Recently, a recombinant canary pox vectored CDV vaccine^g has been licensed for use in ferrets. The vaccine reportedly has been associated with few adverse effects. However, additional studies of this vaccine administered alone and in combination with other vaccines are needed.

^aFervac-D, modified-live avian cell culture CDV vaccine, United Vaccines Inc, Madison, Wis.

^bImrab3, inactivated rabies vaccine, Rhone-Merieux, Athens, Ga.

^cCanine heartworm antigen test, Dirocheck, Synbiotics Corp, San Diego, Calif.

^dDistemink, United Vaccines Inc, Madison, Wis.

^eSmith A, Marshall Farms, North Rose, NY: Personal communication, 2001.

^fStarling D, USDA Center for Veterinary Biologics, Washington, DC: Personal communication, 2001.

^gPure-vax, ferret distemper vaccine, recombinant canary pox vectored, subunit vaccine, Merial, Duluth, Ga.

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