The Journal of Veterinary Medical Science

NOTE

Internal Medicine

Anaphylaxis after vaccination for cats in Japan

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J. Vet. Med. Sci.
84(1): 149–152, 2022
doi: 10.1292/jvms.21-0437

Received: 6 August 2021
Accepted: 29 October 2021
Advanced Epub:
16 November 2021

ABSTRACT. Severe adverse reactions in cats after vaccination were examined from 316 cases reported to the Ministry of Agriculture, Forestry and Fisheries (MAFF) in Japan during 15-year period from April 2004 to March 2019. We found that 130 (41%) showed anaphylaxis, and 99 (76%) of the 130 cases of anaphylaxis resulted in death. Veterinarians should be well prepared to deal with vaccine-associated anaphylaxis in cats. Bovine serum albumin (BSA) as indicator of purification was detected at high levels in commercially available feline vaccines. BSA might derive from fetal calf serum in culture media. This study provides useful information about anaphylaxis including critical details of the potential clinical signs associated with adverse events to feline vaccination.

KEY WORDS: adverse reaction, anaphylaxis, bovine serum albumin, feline vaccine

Although feline vaccines play an important role in the prevention of many infectious diseases in cats, various adverse reactions after vaccination have been observed [9]. Allergic reactions including anaphylaxis are one of the adverse events which can occur after vaccination. Anaphylaxis after vaccination is known to be an immediate-type reaction induced by IgE-mediated type I hypersensitivity [7]. Anaphylaxis is the most severe allergic reaction after vaccination, and Moore *et al.* reported that postvaccination anaphylaxis in some cats resulted in death [10].

There have been multiple reports of anaphylaxis to feline vaccines from many countries. Moore *et al.* reported that in the USA from 2002 to 2005, 1,258,712 doses of vaccine were administered to 496,189 cats, with 17 cats showing anaphylaxis [10]. An epidemiological survey in Canada from 2010 to 2014 identified the rate for anaphylaxis to feline vaccines as 0.029 per 10,000 cats [17]. In the UK, 51 cats were reported to have developed anaphylaxis to vaccines between 1995 and 1999 [4]. Since July 2003, manufacturers and veterinarians in Japan have been required to report all serious adverse reactions (deaths or cases that may lead to death, or diseases and disorders or cases that may lead to them) to drugs and medical devices [5, 6]. In previous study, we collected and reported data on adverse reactions after rabies vaccination in dogs from this database [20]. However, to date, no large-scale investigation has been conducted in Japan on anaphylaxis associated with feline vaccines.

Bovine serum albumin (BSA) is a major component of fetal calf serum (FCS) which is commonly used as culture medium during the production of the vaccine. The World Health Organization (WHO) uses the concentration of BSA in the vaccine as an indicator of the residual amount of FCS used in the production of the vaccine, and for human vaccines, it should be less than 50 ng/dose [19]. On the other hand, we previously demonstrated the presence of specific IgE directed to FCS in sera from dogs that developed allergic reactions after non-rabies mixed vaccination, with many canine vaccines containing high amounts of BSA [13]. Furthermore, immunoblot analysis demonstrated that a variety of FCS components, including albumin, could function as allergens in dogs that developed allergic reactions after vaccination [12]. However, there are no reports of the measurement of BSA levels in feline vaccines.

In this study, we report the results of a large-scale survey of anaphylaxis to feline vaccines in Japan which had occurred over 15-year period from April 2004 through March 2019. Furthermore, we measured BSA levels in feline vaccines. Our results reveal

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(Supplementary material: refer to PMC https://www.ncbi.nlm.nih.gov/pmc/journals/2350/)

useful information about anaphylaxis including critical details of the potential clinical signs associated with adverse events to feline vaccination.

During 15-year period from April 2004 through March 2019, 316 cases of serious adverse reactions, including death, to feline vaccines were reported to the Ministry of Agriculture, Forestry and Fisheries (MAFF) in Japan [6]. The reports not only recorded standard information (breed, sex and neuter status, age, weight, and date of vaccination), but also important factors associated with adverse reactions including type of vaccine, clinical signs, and time to onset postvaccination. In the reports, cats were diagnosed with anaphylaxis by the veterinarians who had administrated the vaccines. In addition, we identified further anaphylaxis cases based on the definition of anaphylaxis as the following clinical signs: collapse, cyanosis, hypothermia, dyspnea, and/or hyperpnea are/is observed within minutes after the vaccination [8]. In Japan, 10 vaccines for cats are commercially available in 2018 (Table 1). Some of these vaccines contain high levels of gelatin (collagen hydrolysate) and casein hydrolysate as protein stabilizers. In addition, 10 vaccines apart from those shown in Table 1 have been used in the past, but these are no longer available.

Adverse reactions to feline vaccines were reported to the adverse event reporting system of the MAFF in Japan (Table 2). The incidence of these adverse reactions could not be calculated because the overall number of vaccine doses was unknown. Of the 316 severe adverse reactions after vaccination, 130 cats showed anaphylaxis, with 99 (76%) of the 130 cases resulting in death. Furthermore, 20 cats were suspected of anaphylaxis but could not be diagnosed due to lack of information on clinical signs, although they died within 1 hr of vaccination (data not shown). In reports from the USA, two out of 17 cats [10], and nine out of 32 cats [7] that developed anaphylaxis to feline vaccines died. There were significant differences in case-fatality rate of anaphylaxis in Japan and that reported in USA ($P<0.01$, χ^2 test). The feline vaccines commercially available in Japan in 2018 are imported from overseas (Table 1). The high mortality rate in cats in Japan to adverse events after vaccination may be due to a lack of awareness and/or appropriate care of feline vaccine-associated anaphylaxis by veterinarians. Alternatively, it may be due to the fact that serious side reactions have become conspicuous due to the postponement of reports of minor side reactions due to lack of legal binding.

There was a significant difference between the age of cats that died of anaphylaxis after vaccination and the age of cats that recovered, and older cats tended to have a higher mortality rate ($P<0.01$, Wilcoxon rank-sum test). One of the possible causes is that older cats have more underlying diseases. Therefore, vaccination of older cats requires more careful follow-up.

Anaphylaxis occurred in both core vaccines (feline viral rhinotracheitis virus, calicivirus and panleukopenia virus) and vaccines

Table 1. Feline vaccines commercially available in Japan as of 2018

Vaccine	Pathogen	Proteins as stabilizer
Nobivac TRICAT[a]	Feline viral rhinotracheitis virus Feline calicivirus Feline panleukopenia virus	Casein (12.5 mg) Gelatin (12.5 mg)
Purevax[b]	Feline viral rhinotracheitis virus Feline calicivirus Feline panleukopenia virus	Casein (4 mg) Collagen (5 mg)
Purevax RCP-FeLV[b]	Feline viral rhinotracheitis virus Feline calicivirus Feline panleukopenia virus Feline leukemia virus	Casein (4 mg) Collagen (5 mg)
Felocell CVR[c]	Feline viral rhinotracheitis virus Feline calicivirus Feline panleukopenia virus	Casein (13.0 mg) Gelatin (10.4 mg)
Fel-O-Vax 3[c]	Feline viral rhinotracheitis virus Feline calicivirus Feline panleukopenia virus	-
Fel-O-Vax 5[c]	Feline viral rhinotracheitis virus Feline calicivirus Feline panleukopenia virus Feline leukemia virus *Chlamydophila felis*	-
Fel-O-Guard Plus 3[c]	Feline viral rhinotracheitis virus Feline calicivirus Feline panleukopenia virus	N-Z-Amine (11 mg) Gelatin (11 mg)
Virbagen CRP[d]	Feline viral rhinotracheitis virus Feline calicivirus Feline panleukopenia virus	Gelatin (6.5 mg)
Fel-O-Vax FIV[c]	Feline immunodeficiency virus	-
Leucogen[d]	Feline leukemia virus	-

[a]MSD Animal Health, [b]Boehringer Ingelheim Animal Health, [c]Zoetis, [d]Virbac.

Table 2. Severe adverse reactions and anaphylaxis to vaccines in cats in Japan

Year	Severe adverse reactions		Anaphylaxis	
	Number of reports	Number of deaths	Number of cases	Number of deaths
2004	6	4	2	2
2005	12	10	6	5
2006	18	16	4	4
2007	16	15	8	8
2008	15	14	7	6
2009	19	16	10	9
2010	19	13	11	9
2011	17	10	7	3
2012	23	18	4	3
2013	21	17	11	8
2014	29	21	9	6
2015	29	20	13	11
2016	25	15	13	7
2017	37	23	14	10
2018	30	20	11	8
Total	316	232	130	99

combined with core and non-core vaccines (feline leukemia virus, *Chlamydophila felis*) (data not shown). However, it should be noted that since there are no statistics on the number of vaccinations, the frequency of adverse reactions is unknown.

Detailed information about 57 cats that showed vaccine-associated anaphylaxis within 1 hr is provided in Supplementary Table 1. Clinical signs can be divided into four major categories: cutaneous, respiratory, cardiovascular, and gastrointestinal [16]. In this study, the reported clinical signs in 35 (61%) cases involved the cardiovascular system (collapse 44%, hypotension 9%, pale visible mucous membrane 9%, bradycardia 7%, hypothermia 7%), in 31 (54%) cases involved the gastrointestinal tract (vomiting 51%, diarrhea 16%), in 41 (72%) cases involved the respiratory tract (dyspnea 30%, cyanosis 12%, tachypnea 37%), and in 6 (11%) cases involved the skin (facial edema 9%, pruritus 2%) (Supplementary Table 1). The clinical signs associated with anaphylaxis in cats reported to the United States Pharmacopeia, Veterinary Practitioners' Reporting Program involved the gastrointestinal tract (66%) (usually vomiting with or without diarrhea), the respiratory tract (22%), and the skin (12%) [7]. Comparing the current study to these results shows similar frequencies for the clinical manifestations of vaccine adverse events in cats in the gastrointestinal tract and skin. In the previous study, 66% of dogs with rabies vaccination and anaphylaxis had cardiovascular symptoms, 38% had gastrointestinal symptoms, and 55% had respiratory symptoms [20]. Compared to anaphylactic symptoms in dogs after rabies vaccination, cats appear to be more prone to gastrointestinal and respiratory symptoms as post-vaccinated anaphylactic symptoms.

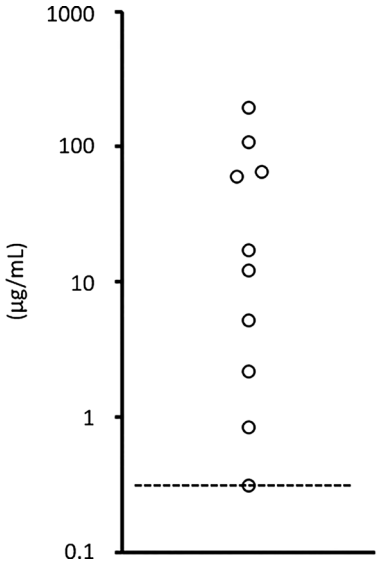

Fig. 1. Bovine serum albumin (BSA) levels in commercially available feline vaccines in Japan. The dotted line represents the detection limit (0.31 μg/ml).

Our previous study reported large amounts of BSA and bovine IgG in canine non-rabies vaccines [13]. On the other hand, the rabies vaccine had a low amount of BSA [20]. In this study, BSA levels in feline vaccines commercially available in Japan were assayed by sandwich ELISA [20]. We found BSA in ten feline vaccines commercially available in Japan and found levels ranging from <0.31 to 196 μg/dose (geometric mean value 12 μg/dose) (Fig. 1). As beef is reported as one of the major allergens for food allergy in cats [11], FCS proteins including BSA might be the cause of vaccine allergies in cats. It was suggested that BSA played an important role in allergic reactions due to vaccination [3]. Van Metre *et al.* reported that ragweed pollen extract containing 0.1–10 μg of Amb a 1 protein, a major allergen, caused systemic allergic reactions in some patients in immunotherapy for ragweed pollinosis [18]. It might be possible that anaphylaxis following vaccinations is caused by residual allergen at several μg levels. BSA in vaccines derives from FCS in culture media used for the growth of vaccine strains of viruses. WHO has recommended that the BSA content as an indicator of purification of medium components of vaccines for humans should be less than 50 ng/dose [19]. It seems desirable that vaccine manufacturers should strive to reduce BSA levels as an indicator of the residual amount of FCS used in the vaccine production.

Factors known to cause allergic reactions to vaccines include proteins as stabilizers, and residues from tissue culture used in vaccine production [1]. Table 1 shows that some of the feline vaccines commercially available in Japan contain large amounts of gelatin (collagen hydrolysate has the same components as gelatin) and casein hydrolysate, also contained within many canine vaccines [13]. Previously, we reported that many children in Japan showed anaphylaxis to human vaccines containing gelatin [14, 15]. In addition, in another study we found that dogs that showed anaphylaxis to canine vaccines had serum IgE directed to gelatin and casein, included in the vaccines as stabilizers [13]. Hence, it seems desirable that vaccine manufacturers should strive to reduce the levels of stabilizers included in feline vaccines.

We found that 99 cats died from anaphylaxis to feline vaccines in Japan. The use of antihistamines or anti-inflammatory doses of glucocorticoids prevaccination is acceptable and does not interfere with the vaccinal immune response [2]. The most important management consideration for cats with anaphylaxis is to be alert to the clinical signs, and to have immediate access to treatment including fluid therapy and epinephrine. In addition, considering that in our study 41 (72%) cases of allergic reactions involved the respiratory tract, it may be necessary to secure an airway. In order to save the life of cats with vaccine-associated anaphylaxis, veterinarians should always be well prepared. Furthermore, the adverse event reporting systems used in this study demonstrated the importance of reporting, recording, and monitoring suspected adverse events following veterinary vaccination.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

ACKNOWLEDGMENT. This study was supported by the Ministry of Education, Culture, Sports, Science and Technology-Supported Program for the Private University Research Branding Project, 2016–2020.

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