Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Veterinary Immunology and Immunopathology 104 (2005) 249–256
Veterinary immunology and immunopathology
www.elsevier.com/locate/vetimm

IgE reactivity to vaccine components in dogs that developed immediate-type allergic reactions after vaccination

Keitaro Ohmori[a,*], Kenichi Masuda[b], Sadatoshi Maeda[a], Yukiko Kaburagi[b], Keigo Kurata[b], Koichi Ohno[a], Douglas J. DeBoer[c], Hajime Tsujimoto[a], Masahiro Sakaguchi[b]

[a]*Department of Veterinary Internal Medicine, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan*
[b]*Laboratory for Allergy Regulation, Research Center for Allergy and Immunology, Yokohama Institute, RIKEN, Yokohama, Japan*
[c]*Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI, USA*

Received 11 March 2004; received in revised form 18 October 2004; accepted 2 December 2004

Abstract

Allergic reactions after vaccination are considered as an important practical problem in dogs; however, their immunological mechanism has not been well understood. The present study was designed to investigate the relationship between IgE reactivity to the vaccines and immediate-type allergic reactions after vaccination in dogs. Sera from 10 dogs that developed immediate-type allergic reactions such as circulatory collapse, cyanosis, dyspnea, facial edema, and vomiting within 1 h after vaccination with non-rabies monovalent or combined vaccines and sera from 50 dogs that did not develop allergic reactions after vaccination were collected. Serum IgE reactivity to the injected vaccines was measured by fluorometric ELISA using a mouse monoclonal anti-dog IgE antibody. Then, IgE reactivity to fetal calf serum (FCS) and stabilizer proteins (gelatin, casein, and peptone) included in the vaccines was measured in sera that had high levels of IgE to the vaccines. Levels of serum specific IgE to the vaccines in dogs with immediate-type allergic reactions (59–4173 fluorescence units [FU], mean ± S.D.: 992.5 ± 1181.9 FU) were significantly higher than those in control dogs (38–192 FU, 92.4 ± 43.3 FU) ($P < 0.001$). Of the eight dogs that developed immediate-type allergic reactions and had high levels of serum specific IgE to the vaccines, seven had specific IgE directed to FCS. The IgE reactivity to the vaccines in sera from these dogs was almost completely inhibited by FCS. The other one dog had serum IgE directed to gelatin and casein included in the vaccine as stabilizers. The results obtained in this study suggest that immediate-type allergic reactions after vaccination in dogs were induced by type I hypersensitivity mediated by IgE directed to vaccine components. In addition, FCS, gelatin, and casein included in vaccines could be the causative allergens that induced immediate-type allergic reactions after vaccination in dogs.

Keywords: Allergy; Anaphylaxis; Dog; IgE; Vaccine

* Corresponding author. Tel.: +81 3 5841 5419; fax: +81 3 5841 8178.
E-mail address: aa27150@mail.ecc.u-tokyo.ac.jp (K. Ohmori).

0165-2427/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetimm.2004.12.003

1. Introduction

Vaccines for infectious diseases in dogs including canine distemper, canine parvovirus infection, canine infectious hepatitis, and leptospirosis are widely used in small animal practice. Although canine vaccines play a very important role in prevention of the infectious diseases, various adverse reactions after vaccination have been observed in dogs (Brooks, 1991; Greene, 1998; Roth, 1999; Gaskell et al., 2001). Allergic reactions including anaphylaxis are one of the problematic adverse events after vaccination. Anaphylaxis after vaccination is known to be an immediate-type reaction induced by IgE-mediated type I hypersensitivity (Greene, 1998). Clinical signs of type I hypersensitivity in dogs after vaccination include hypotensive shock, dyspnea, facial edema, pruritus, weakness, and diarrhea (Greene, 1998). Anaphylaxis is the most severe reaction after vaccination, and it was reported that post-vaccination anaphylaxis resulted in death in some dogs (Ohmori et al., 2002). Allergic reactions after vaccination are considered as an important practical problem in dogs; however, their immunological mechanism has not been well understood.

Occurrence of immediate-type allergic reactions after vaccination has been shown in humans (Zimmerman and Zimmerman, 1998). It was reported that a patient who showed anaphylaxis after vaccination with measles–mumps–rubella (MMR) vaccine had serum IgE directed to gelatin included as a stabilizer in the MMR vaccine (Kelso et al., 1993). In the subsequent study, many children who developed systemic immediate-type allergic reactions after vaccination were shown to have anti-gelatin IgE in their sera (Sakaguchi et al., 1995). These results suggest that most of the allergic reactions after vaccination in humans were mediated by IgE directed to gelatin included as a stabilizer in vaccines for humans.

In this study, to elucidate the relationship between IgE reactivity to the vaccines and immediate-type allergic reactions after vaccination in dogs, levels of specific IgE to the vaccines were measured in the sera from dogs that developed immediate-type allergic reactions after vaccination in comparison to those in the sera from control dogs. Furthermore, we examined the sera for the presence of IgE directed to fetal calf serum (FCS) and stabilizer proteins included in the vaccines for dogs.

2. Materials and methods

2.1. Dogs

Serum samples from 10 dogs that developed immediate-type allergic reactions such as circulatory collapse, cyanosis, dyspnea, facial edema, and vomiting within 1 h after vaccination were collected by small animal practitioners in Japan from January 2001 to July 2002. The serum samples were collected within 1 month after the occurrence of immediate-type allergic reactions after vaccination because levels of serum IgE to vaccines were shown to be decreased several months after vaccine injections in children with immediate-type post-vaccination allergic reactions (Sakaguchi et al., 1997b). As negative controls, serum samples from 50 dogs that had not developed any adverse reactions after vaccination were similarly collected within 1 month after vaccination.

2.2. Vaccines

Four commercially available groups of vaccines exist in Japan. Group 1 vaccines include a monovalent live canine parvovirus vaccine. Group 2 vaccines include monovalent inactivated canine parvovirus or leptospira vaccines. Group 3 vaccines include combined live vaccines composed of canine parvovirus, canine distemper virus, canine adenovirus type 2, and/or canine parainfluenza virus. Group 4 vaccines include combined live (canine parvovirus, canine distemper virus, canine adenovirus type 2, canine parainfluenza virus, and/or canine coronavirus) and inactivated (canine coronavirus and/or leptospira) vaccines. Vaccines produced by four manufacturers (B, C, D, and E) contain gelatin, casein, and/or peptone as protein stabilizers, but those produced by manufacturer A did not contain any stabilizers (Table 1).

2.3. Colorimetric sandwich ELISA for measurement of the amounts of bovine serum albumin (BSA) and bovine IgG contents in vaccines

The amounts of BSA and bovine IgG contents in vaccines were assayed by colorimetric sandwich ELISA. A microplate (Immulon 2, Dynatech, Chantilly, VA) was coated with rabbit anti-BSA IgG (5 μg/

Table 1
Protein contents as stabilizers in non-rabies vaccines commercially available in Japan

Manufacturer	Group of vaccine[a]	Proteins as stabilizers (mg/dose)		
		Gelatin	Casein	Peptone
A	1	–	–	–
	2	–	–	–
	3	–	–	–
	4	–	–	–
	4	–	–	–
B	2	–	–	–
	3	37.5	–	24.38
	3	10	–	9
	4	10	–	9
C	1	–	10	–
	4	18	18	–
D	1	12.5	–	–
	2	–	–	–
	3	12.5	12.5	–
	3	12.5	12.5	–
	4	12.5	12.5	–
E	1	–	–	–
	3	11	8.8	–
	4	11	8.8	–

—: not included in the vaccines.

[a] Group 1 vaccines: monovalent live canine parvovirus vaccines, Group 2 vaccines: monovalent inactivated canine parvovirus or leptospira vaccines, Group 3 vaccines: combined live vaccines composed of canine parvovirus, canine distemper virus, canine adenovirus type 2, and/or canine parainfluenza virus, Group 4 vaccines: combined live (canine parvovirus, canine distemper virus, canine adenovirus type 2, canine parainfluenza virus, and/or canine coronavirus) and inactivated (canine coronavirus and/or leptospira) vaccines.

ml) (Yagai, Yamagata, Japan) or rabbit anti-bovine IgG (5 μg/ml) (Bethyl Laboratories, Montgomery, TX) and incubated for 3 h at 37 °C. After washing, serially diluted vaccines were added to the wells and the microplate was incubated overnight at 4 °C. The microplate was washed, and biotinylated rabbit anti-BSA IgG (Yagai, Yamagata, Japan) or peroxidase-conjugated rabbit anti-bovine IgG (ICN Pharmaceuticals, Aurora, OH) was then added. The microplate was incubated for 1 h at room temperature. In the sandwich ELISA for BSA, peroxidase-conjugated streptavidin (Sigma Chemical, MO) was added after washing, and the microplate was incubated for 1 h at room temperature. The colorimetric reaction was then developed by adding a mixture of hydrogen peroxide and orthophenylenediamine dihydrochloride. After the enzymatic reaction was stopped by adding 4N sulfuric acid, the absorbance at 492 nm was measured with a colorimetric microplate reader (Flow Laboratories, McLean, VA).

2.4. Fluorometric indirect ELISA for detection of serum IgE directed to the vaccines and vaccine components

Serum specific IgE directed to the vaccines, FCS, bovine and porcine gelatin (Sigma Chemical, MO), casein enzymatic hydrolysates (Remel, Lenexa, KS), and bactopeptone (Difco Laboratories, Sparks, MD) was assayed by fluorometric ELISA using a mouse monoclonal anti-dog IgE antibody (DeBoer et al., 1993) according to the previous reports (Sakaguchi et al., 1997a, 2001).

This ELISA was also carried out with non-coated wells using sera from 50 negative control dogs, and these blanks as background-binding effects were subtracted from the measured values for the samples. Cut-off values were defined as follows: mean of IgE levels (fluorescence units, FU) to the injected vaccines of control dogs plus three standard deviations (S.D.).

2.5. Inhibition of serum specific IgE to the vaccines by FCS

The relationship of specific IgE for vaccines with that for FCS was analyzed by fluorometric ELISA inhibition as described previously (Sakaguchi et al., 2001). In the present study, serum specific IgE directed to the vaccine was inhibited by the vaccine or FCS (100 μg/ml) as an inhibitor. The percentage of inhibition was calculated as follows:

$$\left(1 - \frac{\text{FU in the presence of an inhibitor}}{\text{FU in the absence of an inhibitor}}\right) \times 100 = \text{percentage of inhibition}$$

2.6. Statistical analysis

The unpaired two-group *t*-test was used to evaluate differences between the study groups. The result was considered statistically significant when $P < 0.05$.

3. Results

3.1. Dogs that developed immediate-type allergic reactions after vaccination

Table 2 shows clinical findings for 10 dogs that developed apparent immediate-type allergic reactions including anaphylaxis within 1 h after vaccination. The breeds of the 10 dogs consisted of miniature dachshund (five dogs), pug (two), miniature schnauzer (one), toy poodle (one), and welsh corgi (one). The ages of the 10 dogs ranged from 2 months to 3 years (mean ± S.D., 10 months ± 1 year). There were six males and four females. Of the 10 dogs, nine were injected with combined vaccines (Group 3 or 4), and the other one was a monovalent vaccine (Group 1). The onset time of clinical signs ranged from 1 to 60 min (mean time ± S.D., 22 ± 20 min). Five (numbers 2, 6, 7, 8, and 10) of the 10 dogs showed cardiovascular and/or respiratory signs, and the others (numbers 1, 3, 4, 5, and 9) manifested dermatological signs such as facial edema. The number of previous vaccinations prior to the vaccination that provoked the allergic reactions was 1–4 in seven dogs; however, three dogs (numbers 2, 4, and 8) had never received a vaccination.

3.2. Serum IgE reactivity to the injected vaccines

We measured the levels of specific IgE directed to the injected vaccines in the sera from 10 dogs that developed immediate-type allergic reactions and in the sera from 50 dogs without any adverse reactions after vaccination (Fig. 1). Of the 10 dogs, eight had high levels of specific IgE to the vaccines in their sera. The 50 control dogs had no or low levels of specific

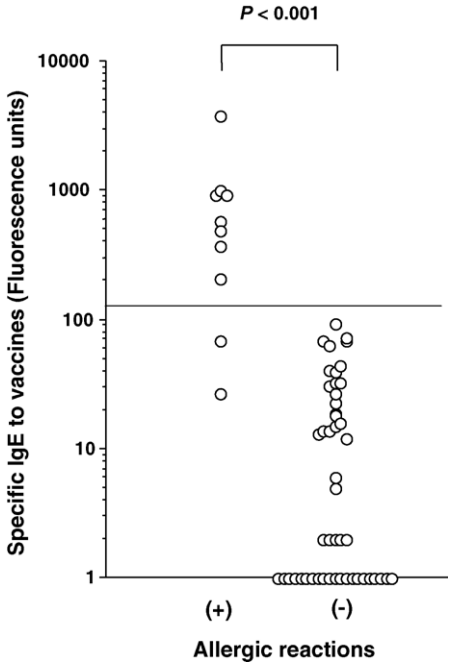

Fig. 1. IgE reactivity to the injected vaccines in the sera from 10 dogs that developed immediate-type allergic reactions after vaccination (+) and in the sera from 50 dogs without any adverse reactions after vaccination (—). Each dot represents the IgE level of each dog. Horizontal bar indicates the geometric mean of IgE levels of control dogs plus 3 S.D.

Table 2
Clinical findings for dogs that developed immediate type-allergic reactions after vaccination

Dog number	Breed	Age	Sex	Group of the injected vaccine	Number of previous vaccination	Onset time after vaccination (min)	Clinical signs
1	M. schnauzer	3 months	F	4	2	40	Facial edema
2	Toy poodle	3 months	F	3	0	15	Cyanosis, vomiting
3	M. dachshund	5 months	M	4	1	60	Facial edema
4	M. dachshund	2 months	M	3	0	30	Facial edema
5	Pug	2 years 4 months	M	3	4	30	Facial edema, pruritus
6	M. dachshund	3 years	M	3	4	5	Circulatory collapse, cyanosis, dyspnea, bradycardia
7	Pug	2 months	M	3	1	2	Cyanosis, hypotension, dyspnea
8	Welsh corgi	3 months	M	4	0	1	Circulatory collapse, bradycardia
9	M. dachshund	4 months	F	1	1	30	Angioedema around eyes
10	M. dachshund	1 year 5 months	F	4	3	5	Hypotension, vomiting

M. schnauzer: Miniature schnauzer, M. dachshund: Miniature dachshund, F: female, M: male.

Table 3
Amounts of bovine serum albumin (BSA) and bovine IgG contents in vaccines for dogs commercially available in Japan

Manufacturer	Group of vaccine	Vaccine		Live component		Inactivated component	
		BSA (μg/dose)	IgG (μg/dose)	BSA (μg/dose)	IgG (μg/dose)	BSA (μg/dose)	IgG (μg/dose)
A	2	87.3 ± 23.3	2.0 ± 0.76	–	–	87.3 ± 23.3	2.0 ± 0.76
	3	61.6 ± 2.5	1.6 ± 0.23	61.6 ± 2.5	1.6 ± 0.23	–	–
	4	85.8 ± 8.3	2.7 ± 1.2	73.4 ± 6.1	2.7 ± 1.2	14.1 ± 0.93	<0.04
	4	87.3 ± 25.0	2.8 ± 0.31	83.3 ± 25.0	2.8 ± 0.31	4.1 ± 1.1	<0.04
B	3	161 ± 73.4	3.8 ± 0.95	161 ± 73.4	3.8 ± 0.95	–	–
	4	2313 ± 1408	4.5 ± 2.2	206 ± 85.2	4.3 ± 2.4	2083 ± 1325	0.21 ± 0.03
C	4	3678 ± 1765	13.3 ± 2.1	9.6 ± 3.5	8.7 ± 2.4	3669 ± 1763	2.3 ± 0.90
D	3	241 ± 24.0	3.0 ± 1.0	241 ± 24.0	3.0 ± 1.0	–	–
	4	1642 ± 1197	3.7 ± 3.2	475 ± 585	3.7 ± 3.2	1166 ± 655	<0.04

—: the vaccines do not contain live or inactivated component.

IgE to the vaccines in their sera. Serum levels of specific IgE to the vaccines in 10 dogs with immediate-type allergic reactions (59–4173 FU, mean ± S.D.: 992.5 ± 1181.9 FU) were significantly higher than those in 50 dogs without any adverse reactions after vaccination (38–192 FU, 92.4 ± 43.3 FU) ($P < 0.001$).

3.3. Amounts of BSA and bovine IgG contents in vaccines

We measured amounts of BSA and bovine IgG contents in vaccines (Table 3). These contents were measured for more than three lots of each commercially available vaccine. Group 2 vaccines produced by manufacturer A contained 87.3 ± 23.3 μg of BSA and 2.0 ± 0.76 μg of bovine IgG per dose. Group 3 vaccines produced by three manufacturers contained BSA ranging from 61.6 ± 2.5 to 241 ± 24.0 μg/dose (mean value ± S.D., 154 ± 90 μg/dose) and bovine IgG ranging from 1.6 ± 0.23 to 3.8 ± 0.95 μg/dose (2.8 ± 1.1 μg/dose). Group 4 vaccines produced by four manufacturers contained BSA ranging from 85.8 ± 8.3 to 3678 ± 1765 μg/dose (1561 ± 1533 μg/dose) and bovine IgG ranging from 2.7 ± 1.2 to 13.3 ± 2.1 μg/dose (5.4 ± 4.5 μg/dose). The inactivated part of Group 4 vaccines produced by manufacturers B, C, and D contained extremely high amounts of BSA (more than 1 mg/dose).

3.4. Serum IgE reactivity to specific proteins included in vaccines

To elucidate the relationship between some proteins included in vaccines and immediate-type allergic reactions after vaccination, we measured specific IgE directed to FCS, gelatin, casein, and bactopeptone in the sera from eight dogs that had high

Table 4
Serum IgE reactivity to vaccine components in dogs that had specific IgE to the injected vaccines

Dog number	IgE reactivity					
	Vaccine	FCS	Bovine gelatin	Porcine gelatin	Casein	Peptone
1	++	++	NT	NT	NT	NT
2	++	+++	NT	NT	NT	NT
3	++	+	NT	NT	NT	NT
4	++	++	–	–	–	NT
5	+	+++	–	–	NT	–
6	++	+	–	–	NT	–
7	+++	++	NT	NT	NT	NT
8	++	–	++	+++	+++	NT

FCS: fetal calf serum, NT: not tested, because the injected vaccines did not contain the stabilizers, +++: 1000 ≤ FU, ++: 300 ≤ FU < 1000, +: 100 ≤ FU < 300, —: FU < 100.

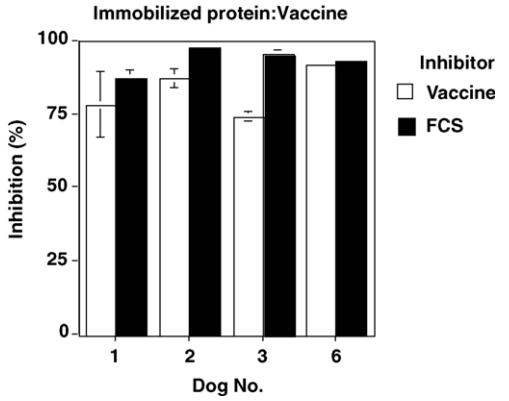

Fig. 2. Inhibition of serum IgE reactivity to vaccines by fetal calf serum (FCS). Data are expressed as mean ± S.D.

levels of serum IgE directed to the vaccines (Table 4). Of the eight dogs, seven had specific IgE directed to FCS, and one (number 8) had specific IgE directed to gelatin and casein included as stabilizers in vaccines.

3.5. Inhibition of serum IgE reactivity to vaccines by FCS

To examine whether specific IgE to vaccines recognize proteins derived from FCS, ELISA inhibition for specific IgE to the injected vaccines was carried out using FCS as an inhibitor (Fig. 2). When the serum samples (numbers 1, 2, 3, and 6) were pre-incubated with the vaccine before the ELISA, specific IgE to the vaccine was almost completely abolished. When the serum samples were pre-incubated with FCS before the ELISA, specific IgE to the vaccines was also almost completely abolished. We could not carry out ELISA inhibition in dog numbers 4, 5, and 7 because of the limited amount of their serum samples.

4. Discussion

In the present study, large amounts of BSA and bovine IgG, μg order per dose, were shown to be included in the monovalent and combined vaccines for dogs examined. As for the vaccines for humans, the World Health Organization (WHO) proposed that BSA content in vaccines should be less than 50 ng/dose (WHO, 1994). BSA and bovine IgG in vaccines might be derived from FCS in culture media for the growth of vaccine strains of viruses. Moreover, the inactivated part of Group 4 vaccines produced by some vaccine manufacturers included extremely large amounts of BSA, mg order per dose. Such a large amount of BSA might be derived from the culture media for leptospira.

To elucidate the relationship between the injected vaccines and immediate-type allergic reactions after vaccination in dogs, we measured specific IgE directed to the injected vaccines in the sera from 10 dogs that developed immediate-type allergic reactions after vaccination. Eight of the 10 dogs had apparently high levels of serum specific IgE to the injected vaccines compared with control dogs, indicating that these dogs were sensitized to some proteins included in vaccines. On the other hand, two (numbers 9 and 10) of the 10 dogs did not have high serum IgE levels to the vaccines. In humans, it was reported that some children who exhibited apparent immediate-type allergic reactions after vaccination did not have serum specific IgE to gelatin (Sakaguchi et al., 1995, 1996). The immunological mechanism underlying the reactions in the two dogs has not yet been clarified.

To investigate the causative vaccine component(s) that induced immediate-type allergic reactions, we measured specific IgE to FCS and stabilizer proteins in the sera from eight dogs that had high levels of specific IgE to the injected vaccines. Seven of the eight dogs had serum specific IgE to FCS. Furthermore, the serum IgE reactivity to the vaccine was almost completely inhibited by FCS. In this study, we also revealed that vaccines for dogs contained large amounts of BSA and bovine IgG derived from FCS. From these findings, most of the allergic reactions after vaccination in dogs might be caused by FCS derived from the culture media used for the production of vaccines. FCS contains a variety of proteins including BSA, fibrinogen, lipoprotein, macroglobulin, and transferrin. Although it was reported that vaccination with rabies vaccine induced the elevation of the serum IgE specific to the vaccine antigens including BSA and bovine fibronectin in some healthy dogs (Hogenesch et al., 2002), at present, there has been no data on the specific protein(s) included in FCS to cause allergic reactions after vaccination in dogs. Further studies are necessary to identify the causative protein(s) included in FCS that induce allergic reactions after vaccination in dogs.

One dog (number 8) had specific IgE to gelatin and casein as stabilizers included in the vaccine, but did not have specific IgE to FCS in the serum. In humans, most of the immediate-type allergic reactions after vaccination were shown to be caused by gelatin included in the vaccines (Kelso et al., 1993; Sakaguchi et al., 1995). In addition, casein is one of the major allergens in milk allergy in humans (Sampson, 1998). In dogs, allergic reactions to milk were also reported (Jeffers et al., 1996). These results suggest that gelatin and casein included in the vaccine might have induced the immediate-type allergic reactions after vaccination in dog number 8.

In this study, three dogs exhibited immediate-type allergic reactions after the first vaccination and had high levels of serum IgE to FCS or protein stabilizers such as gelatin and casein included in vaccines, suggesting that these dogs might have been already sensitized to FCS, gelatin, or casein included in vaccines prior to the first vaccination. In humans, some children who showed allergic reactions after vaccination also manifested immediate-type allergic reactions to food containing gelatin before the vaccination (Sakaguchi et al., 1996). Moreover, in dogs, beef is known to be a predominant food that cause food allergy (Jeffers et al., 1996). From these findings, the dogs that showed allergic reactions after the first vaccination might have been already sensitized to beef allergens. It is unclear when these dogs were sensitized to FCS, gelatin, or casein. In humans, it was reported that a baby developed egg allergy after consumption of large amounts of eggs by the mother during pregnancy and breast-feeding (Reininger et al., 2003). In our study, when the dogs were 2–3 months old, they exhibited allergic reactions after the first vaccination. It may be possible that prenatal uptake of beef allergens and/or uptake of beef allergens during breast-feeding contributed to the sensitization of FCS, gelatin, or casein. On the other hand, in other dogs that showed allergic reactions after several vaccinations, it is unclear whether these dogs had been sensitized to FCS, gelatin, or casein by previous vaccination or other routes. Further study will be needed to investigate the relationship between post-vaccination allergic reactions and other allergic diseases, especially food allergy, in dogs.

Finally, we revealed the presence of the large amounts of FCS content in vaccines for dogs, and most of the dogs that developed immediate-type allergic reactions after vaccination had high levels of serum IgE directed to FCS. Most of the vaccines for dogs commercially available in Japan are manufactured in the US and Europe. It is advisable that vaccine manufacturers put more effort into reducing the amounts of FCS and BSA included in vaccines for dogs. Large amounts of gelatin, casein, and bacto-peptone are also included as stabilizers in most of the vaccines for dogs. In this study, one dog that developed immediate-type allergic reactions after vaccination had serum specific IgE to gelatin and casein. Although the frequency of the allergic reactions caused by protein stabilizers such as gelatin and casein included in vaccines could be low, it is also recommended that vaccine manufacturers should eliminate the amounts of these protein stabilizers from vaccines or replace them with other low-allergenic stabilizers.

Acknowledgement

The authors thank private practitioners who provided the serum samples and Dr. Morimasa Yamanaka in Kyoto Biken Laboratories, Inc. for his assistance in collecting the serum samples. This study was supported by a grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

Brooks, R., 1991. Adverse reactions to canine and feline vaccines. Aust. Vet. J. 68, 342–344.

DeBoer, D.J., Ewing, K.M., Schulyz, K.T., 1993. Production and characterization of mouse monoclonal antibodies directed against canine IgE and IgG. Vet. Immunol. Immunopathol. 37, 183–199.

Gaskell, R.M., Gettinby, G., Graham, S.J., Skilton, D., 2001. The suspected adverse reactions (SAR) surveillance scheme (SARSS) and review of suspected adverse reactions data. In: Gaskell, R.M., Gettinby, G., Graham, S.J., Skilton, D. (Eds.), Veterinary Products Committee (VPC) Working Group on Feline and Canine Vaccination. Final Report to the VPC. Department for Environment, Food & Rural Affairs, London, pp. 29–62.

Greene, C.E., 1998. Immunoprophylaxis and Immunotherapy. In: Greene, C.E. (Ed.), Infectious Diseases of the Dog and Cat. 2nd ed. WB Saunders, Philadelphia, pp. 717–750.

Hogenesch, H., Dunham, A.D., Scott-Moncrieff, C., Glickman, L.T., DeBoer, D.J., 2002. Effect of vaccination on serum concentrations of total and antigen-specific immunoglobulin E in dogs. Am. J. Vet. Res. 63, 611–616.

Jeffers, J.G., Meyer, E.K., Sosis, E.J., 1996. Responses of dogs with food allergies to single-ingredient dietary provocation. J. Am. Vet. Med. Assoc. 209, 608–611.

Kelso, J.M., Jones, R.T., Yunginger, J.W., 1993. Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin. J. Allergy Clin. Immunol. 91, 867–872.

Ohmori, K., Masuda, K., Sakaguchi, M., Kaburagi, Y., Ohno, K., Tsujimoto, H., 2002. A retrospective study on adverse reactions to canine vaccines in Japan. J. Vet. Med. Sci. 64, 851–853.

Reininger, R., Exner, H., Kuderna, C., Rumpold, H., Balic, N., Valenta, R., Spitzauer, S., 2003. Possible modes of allergen-specific sensitization and boosting in an atopic child. Int. Arch. Allergy Immunol. 130, 275–279.

Roth, J.A., 1999. Mechanistic bases for adverse vaccine reactions and vaccine failures. Adv. Vet. Med. 41, 681–700.

Sakaguchi, M., Ogura, H., Inouye, S., 1995. IgE antibody to gelatin in children with immediate-type reactions to measles and mumps vaccines. J. Allergy Clin. Immunol. 96, 563–565.

Sakaguchi, M., Nakayama, T., Inouye, S., 1996. Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines. J. Allergy Clin. Immunol. 98, 1058–1061.

Sakaguchi, M., Nakano, T., Tsujimoto, H., Sasaki, Y., DeBoer, D.J., Inouy, S., 1997a. Fluorometric ELISA for allergen-specific dog IgE antibody. Allergol. Int. 46, 207–212.

Sakaguchi, M., Yoshida, T., Asahi, T., Aoki, T., Miyatani, Y., Inouye, S., 1997b. Development of IgE antibody to gelatin in children with systemic immediate-type reactions to vaccines. J. Allergy Clin. Immunol. 99, 720–721.

Sakaguchi, M., Masuda, K., Yasueda, H., Saito, S., DeBoer, D.J., Tsujimoto, H., 2001. IgE reactivity and cross-reactivity to Japanese cedar (*Cryptomeria japonica*) and cypress (*Chamaecyparis obtusa*) pollen allergens in dogs with atopic dermatitis. Vet. Immunol. Immunopathol. 83, 69–77.

Sampson, H.A., 1998. Adverse reactions to foods. In: Middleton, E., Reed, C.E., Ellis, E.F., Adkinson, N.F., Yunginger, J.W., Busse, W.W. (Eds.), Allergy: Principles and Practice. 5th ed. Mosby, St. Louis, pp. 1162–1182.

WHO, 1994. Requirements for measles, mumps, and rubella vaccines and combined vaccine (live). In: WHO (Ed.), WHO Technical Report Series, vol. 840, pp. 109–117.

Zimmerman, B., Zimmerman, R.S., 1998. Adverse reactions to vaccines. In: Middleton, E., Reed, C.E., Ellis, E.F., Adkinson, N.F., Yunginger, J.W., Busse, W.W. (Eds.), Allergy: Principles and Practice. 5th ed. Mosby, St. Louis, pp. 1199–1211.