FULL PAPER

Surgery

Incidence of anaphylactic reactions after propofol administration in dogs

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ABSTRACT. Propofol is an anesthetic agent suspended in an emulsion system that includes egg yolk lecithin and soybean oil, because of which, there is concern about the use of propofol in patients allergic to these substances. We examined the association between propofol administration and incidence of adverse events in dogs with allergy to egg yolk lecithin and soybean oil. On the basis of the findings of an allergen-specific immunoglobulin E (IgE) test, 14 dogs with high levels (high-IgE group) and 7 dogs with low levels (normal-IgE group) of IgE were selected. Following intravenous administration of propofol, the incidence of anaphylactic reactions and plasma histamine concentrations under general anesthesia maintained with isoflurane throughout surgery were compared between the two groups. The frequency of anaphylactic reactions and plasma histamine concentrations were compared by the chi-square test and Student t-test, respectively. The statistical significance for both tests was set at $P<0.05$. In the high- and normal-IgE groups, the average frequencies of anaphylactic reactions after propofol administration were 21.4 and 14.3%, and the mean plasma histamine concentrations were 167.9 ± 94.5 nM and 65.7 ± 40.3 nM, respectively. Animals of neither groups experienced shock-like symptoms. These results revealed that propofol might be relatively safe, although careful perioperative anesthesia monitoring and standby protocols are required when using propofol in dogs with a history of allergic diseases or high chicken- or soybean-specific IgE levels.

KEY WORDS: anesthesia, dog, histamine, immunoglobulin-E, propofol-induced anaphylaxis

Anaphylaxis is defined as "a potentially fatal hypersensitive reaction to the invasion of an allergen or other substance that causes systemic allergic symptoms in multiple organs" and anaphylactic shock as "hypotension or impaired consciousness associated with anaphylaxis" [24].

Propofol is widely used for canine anesthesia [19]. In human medicine, administration of propofol to patients allergic to eggs or soy protein is either contraindicated or requires careful handling by the anesthesiologist [3, 30]. In dogs, comprehensive precautions must also be taken against anaphylactic reaction as a form of toxicity during anesthesia, including during the use of injectable anesthetics. However, other than expressions of concern regarding the effect of allergic reaction during intradermal tests, there are no reports of propofol-induced anaphylaxis till date [6, 19].

The main allergens responsible for immunoglobulin (Ig) E-mediated food allergy in dogs are beef, chicken, cow milk, eggs, maize, soy and rice, in that order [10]. Additionally, cross-reactions between chicken and eggs (yolk and white) are known to occur [11]. In addition to foods containing proteins as main ingredients, caution is also required with respect to those containing traces of protein as secondary ingredients; soybean oil, described as being "allergen-free", has been found to contain residual protein [22], and severely soy-allergic human patients might experience a hypersensitive reaction to trace amounts of soy protein in soybean oil or soy lecithin [2, 7]. Therefore, in dogs, caution is required with respect to the development of perioperative anaphylaxis, which is classified as IgE-mediated allergic anaphylaxis [18] induced by purified egg phosphatide (lecithin) or soy protein in fatty excipients in propofol.

In a large-scale study of anesthesia-associated accidents in humans, including 1,284,957 cases, the Japanese Society of

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Table 1. The Characteristics profile of the high IgE group (Nn=14)

Case	Sex	Age (year)	Breed	Operation	Allergen-specific IgE Test				Anamnesis (allergy)
					Egg white	Yolk	Chicken	Soy	
1	Male	11.2	Welsh Corgi Pembroke	Sterilization	0	17	108	148	+
2	Female	1	Yorkshire Terrier	Sterilization	47	9	31	105	+
3	Female	7	Shih Tzu	Sterilization	61	7	193	69	+
4	Male	7	Papillon	Sterilization	212	71	170	102	+
5	Female	2.7	M. Dachshund	Sterilization	6	8	69	163	+
6	Male	1.3	T. Poogle	Sterilization	0	8	43	298	+
7	Male	9	M. Dachshund	Sterilization	26	33	29	150	+
8	Male	11.8	Papillon	Sterilization	81	23	66	111	+
9	Male	3.5	T. Poogle	Sterilization	30	12	140	0	+
10	Male	1.1	Papillon	Sterilization	0	17	45	182	+
11	Male	0.67	Jack Russell Terrier	Sterilization	66	6	48	144	+
12	Male	0.83	G. Retriver	Sterilization	0	0	102	0	−
13	Female	1.67	Cavalier King Charles Spaniel	Sterilization	101	22	28	68	+
14	Female	0.5	Border Collie	Sterilization	73	32	50	108	+
Mean		4.23			50.21	18.93	80.14	117.71	

Anesthesiologists observed a low incidence of perioperative anaphylaxis—1 in 40,000 (approximately 0.0025%), including one case of cardiopulmonary arrest and three of severe hypotension [15]. Muscle relaxants (58.08%) are the most common causative substances of perioperative anaphylaxis, followed by latex (19.65%), antibiotics (12.85%), colloids (3.43%), sedatives (2.34%) and anesthetics (1.69%) [17]; propofol causes anaphylaxis so infrequently that it is not even mentioned among the common causal factors. For dogs, anaphylaxis is listed as an adverse reaction to injectable anesthetics, including, but not limited to, propofol [19]. To our knowledge, no study till date has investigated anaphylaxis following propofol administration in egg- or soy-allergic dogs.

In humans, allergen identification tests in case of anaphylaxis include allergen-specific IgE [14], prick and intradermal tests [5, 14]. Allergen-specific IgE tests, which enable IgE quantification in an equivalent manner to intradermal tests, are now available for dogs as well [21]. In the present study, we drew on this to investigate anaphylaxis after propofol administration in dogs that exhibited high allergen-specific IgE levels against egg white and yolk, chicken cross-reacting with egg white and yolk, and soy protein IgE. We also included a control group of dogs that did not exhibit high IgE levels. Inflammatory mediators released from mast cells and basophils at onset of anaphylaxis are useful for diagnosis of anaphylaxis [15]. Histamines have been shown to be released in IgE-mediated hypersensitivity reactions to food antigens in dogs [8] and a few other animals. Adverse events following propofol administration in dogs could possibly be propofol-induced anaphylactic reactions. Therefore, we evaluated the safety of propofol administration and its association with anaphylactic reactions in dogs by allergen-specific IgE and blood histamine concentration tests.

MATERIALS AND METHODS

This retrospective study included dogs presented at the Onuma Animal Hospital (Saitama) and Oosagami Animal Clinic (Saitama) between October 2010 and March 2015, that tested positive for allergen-specific IgE (Animal Allergy Clinical Laboratories, Sagamihara, Japan) against egg (yolk or white) and chicken cross-reacting with egg yolk or white [21] as well as dogs that exhibited high levels of soy IgE (>100 ng/ml). In 14 of these dogs (high-IgE group), anesthesia was induced with propofol as an ultra-short-acting injectable anesthetic (2.2–6.6 mg/kg; intravenous administration) [19] prior to surgery. In humans with a history of drug-induced allergy, particular caution is required during the initial few min after drug administration, when anaphylaxis is most likely to occur [14, 30]. Therefore, adverse events during the 15 min immediately after propofol administration were monitored. History of allergy was recorded for each animal. When we obtained consent for anesthesia from the owners of animals included in this study, we also obtained consent for performing additional examinations in case of adverse events and for the use of test results for this study. The high IgE group (n=14; male, 5; female, 9; mean age, 4.23 years; age range, 0.5–11.8 years) included 6 animals with allergy to egg or chicken and 10 with soy allergy; 2 dogs (cases 1 and 4) in each subgroup exhibited high IgE levels against the specific antigen. All 14 of these dogs were purebreds, and there was no bias in terms of breed (Table 1). A group of 7 dogs (male, 3; female, 4; mean age, 3.42 years; age range, 0.58–9.0 years) with low egg/chicken and soy IgE concentrations and no bias in terms of breed was included as the negative control group (normal-IgE group; Table 2) and subjected to the same tests as the high-IgE group.

The mean allergen-specific IgE concentrations of dogs that exhibited high IgE concentrations against egg/chicken (n=7; egg white, 7; yolk, 0; multiple allergens, 1) and soy (n=10) were compared with those of dogs that exhibited normal IgE concentrations against egg / chicken (n=15; yolk, 0) and soy (n=11).

In the high-IgE group, plasma histamine concentrations were measured in 4 of the 14 dogs (male and female, 2 each, with no bias in breed; mean age, 0.92 years; age range, 0.5–1.67 years), of which 3 developed adverse drug reactions and 1 exhibited no

Table 2. The Characteristics profile of the normal-IgE group (Nn=7)

Case	Sex	Age (year)	Breed	Operation	Allergen-specific IgE Test				Anamnesis (allergy)
					Egg white	Yolk	Chicken	Soy	
1	Male	0.67	MIX	Sterilization	21	22	46	41	−
2	Male	8	M. Dachshund	Perineocele	71	39	53	77	−
3	Female	0.58	Bernese Mountain Dog	Sterilization	64	5	0	0	−
4	Female	9	A. Cocker Spaniel	Sterilization	2	11	43	19	−
5	Female	1.67	MIX	Sterilization	17	24	53	30	−
6	Male	3	Kerry Blue Terrier	Tumor resection	21	7	20	0	−
7	Female	1	White Suis Shepherd Dog	Sterilization	23	13	69	0	+
Mean		3.42			31.29	17.29	40.57	23.86	

Table 3. Adverse events and plasma histamine concentrations in the high- and normal-IgE groups

	Case	Abnormal symptom of perioperative			Histamine level
		Skin/mucosa	Respiratory	Cardiovascular	
High-IgE group	11	Blush	-	Hypotension	95.1
	12	-	Depression[a]	Hypotension	177.1
	13	-	-	-	101.2
	14	-	Depression[a]	-	298.3
	Mean				167.93
Normal-IgE group	1	-	-	-	51.9
	2	-	-	-	68.6
	3	Blush	-	Hypotension	139.8
	4	-	-	-	18.1
	5	-	-	-	89.2
	6	-	-	-	30.2
	7	-	-	-	62.3
	Mean				65.73

a) Respiratory arrest, hypercapnia.

obvious adverse reaction. In contrast, all 7 of the dogs in the normal-IgE group were evaluated for plasma histamine concentration.

Venous blood samples for evaluation of plasma histamine concentration were collected in tubes containing ethylenediaminetetraacetic acid after propofol administration. On the basis of previous reports that blood histamine concentrations peak approximately 5 min after the onset of anaphylaxis and return to reference levels after 30–60 min [26], we intended to sample venous blood 5 min after propofol administration. However, in practice, sampling was delayed in a few cases (2 dogs each in the high and normal-IgE groups), because of the work involved in securing the airway. Plasma was separated by centrifugation at 1,500 rpm for 10 min and stored at −20°C until measurement of histamine concentrations using a histamine enzyme-linked immunosorbent assay kit (Histamine EIA Kit, Oxford Biomedical Research, Inc., Oxford, U.K.) according to the manufacturer's instructions.

In fur-covered animals, cutaneous signs are even more likely to be missed. Accordingly, flushing of the skin/mucosa, respiratory depression, bradycardia, hypotension and tachycardia were evaluated as adverse events suggestive of anaphylaxis. Ventilation was managed by spontaneous respiration without the use of a ventilator. Respiratory care involved monitoring of the respiratory rate and carbon dioxide concentration.

Treatment during anaphylaxis included fluid infusion and administration of high-flow oxygen and adrenaline (0.0025–0.005 mg/ kg, intravenous). Adjuvant therapy involved administration of glucocorticoids for prevention of late-onset anaphylaxis, antihistamines for treatment of cutaneous symptoms, such as itching, rashes, hives and vascular edema, and H2 blockers, which are considered to be effective in combination with antihistamines [4, 27, 28, 31].

Comparison of frequency of anaphylaxis was performed by the χ^2 test. Comparison of plasma histamine concentrations was performed by Student's *t*-test. Significant differences between the high- and normal-IgE groups were determined at *P*<0.05.

RESULTS

Adverse drug reactions were observed in 3 of the 14 dogs in the high-IgE group (cases 11, 12 and 14; 21.4%). Adverse drug reactions considered as representing anaphylaxis included flushing (n=1), hypotension (n=2) and respiratory depression (n=1; respiratory arrest and high end-tidal carbon dioxide concentration), some of which were observed in the same animals (Table 3). However, all adverse reactions were transient and mild, and since they improved with symptomatic treatment alone and did not

Table 4. Adverse events and plasma histamine concentrations in the adverse event and non-adverse event cases

	Case	Abnormal symptom of perioperative			Histamine level
		Skin/mucosa	Respiratory	Cardiovascular	
Adverse event cases	11	Blush	-	Hypotension	95.1
	12	-	Depression[a]	Hypotension	177.1
	14	-	Depression[a]	-	298.3
	3	Blush	-	Hypotension	139.8
	Mean				177.57[b]
Non-Adverse event cases	1	-	-	-	51.9
	2	-	-	-	68.6
	4	-	-	-	18.1
	5	-	-	-	89.2
	6	-	-	-	30.2
	7	-	-	-	62.3
	13	-	-	-	101.2
	Mean				60.21[b]

a) Respiratory arrest, hypercapnia. b) Significant differences between the adverse and non-adverse event cases were determined at $P<0.05$.

Table 5. Normal scores of the allergen-specific IgE test in the high- and normal-IgE groups

Case	Allergen-specific IgE test		
	Egg white[a]	Chicken	Soy
High IgE			
1	0	—[b]	—[b]
2	47	31	—[b]
3	61	—[b]	69
5	6	69	—[b]
6	0	43	—[b]
7	26	29	—[b]
8	81	66	—[b]
9	30	—[b]	0
10	0	45	—[b]
11	66	48	—[b]
12	0	—[b]	0
13	—[b]	28	68
14	73	50	—[b]
Normal IgE			
1	21	46	41
2	71	53	77
3	64	0	0
4	2	43	19
5	17	53	30
6	21	20	0
7	23	69	0
n	19	16	11
Min	0	0	0
Max	81	69	77

a) Yolk obtained from birds. b) –: Normal IgE score.

Table 6. High IgE scores of the allergen-specific IgE test in the high- and normal-IgE groups

Case	Allergen-specific IgE test		
	Egg white[a]	Chicken	Soy
High IgE			
1	—[b]	108	148
2	—[b]	—[b]	105
3	—[b]	193	—[b]
4	212	170	102
5	—[b]	—[b]	163
6	—[b]	—[b]	298
7	—[b]	—[b]	150
8	—[b]	—[b]	111
9	—[b]	140	—[b]
10	—[b]	—[b]	182
11	—[b]	—[b]	144
12	—[b]	102	—[b]
13	101	—[b]	—[b]
14	—[b]	—[b]	108
n	2	5	10
Min	101	102	102
Max	212	193	298

a) Yolk obtained from birds. b) –: Normal IgE score.

result in anaphylactic shock, no treatment for anaphylaxis was administered. Incidences of flushing and hypertension in the normal-IgE group (14.29%; 1 of 7 dogs) were lower than those in the high-IgE group (21.4%; 3 of 14 dogs; Table 3). The incidences of anamnesis of allergy in the high- and normal-IgE groups were 92.9% (13 of 14 dogs) and 14.29% (1 of 7 dogs), respectively (Tables 1 and 2). Comparison of mean IgE concentrations between the normal- (Table 5) and high- (Table 6) IgE groups revealed that the latter group exhibited higher IgE concentrations for each of the evaluated allergens (egg white, 4.88-fold; chicken, 3.29-fold; and soy, 5.48- fold higher than the corresponding values in the normal-IgE group; Table 7). There were no cases of egg-yolk

Table 7. Mean and multiple proportion of the allergen-specific IgE test in the high- and normal-IgE groups

	High-IgE group			Normal-IgE group		
	Egg white	Chicken	Soy	Egg white	Chicken	Soy
Mean	156.5	142.6	151.1	32.1	43.3	27.6
Multiple proportion[a)]	4.875	3.293	5.475	–	–	–

a) Mean value of the high-IgE group/mean value of the normal IgE-group.
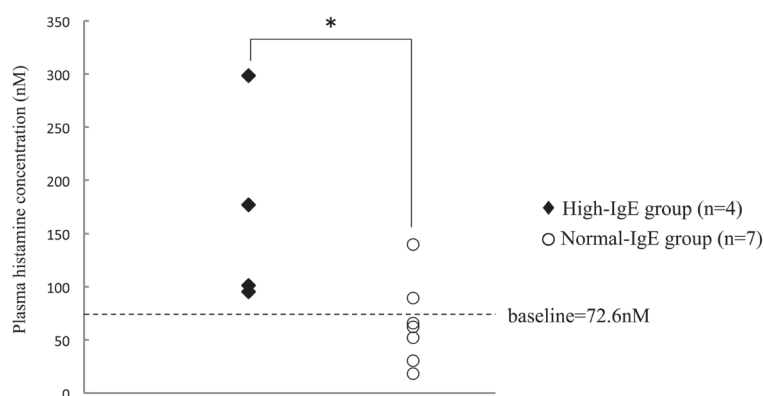
Fig. 1. Plasma histamine concentrations (nM) of the high- (n=4) and normal-(n=7) IgE concentration groups. *$P<0.05$, significant intergroup differences.

allergy in the high-IgE group.

The mean serum histamine concentration of the high-IgE group (167.93 nM; range, 95.1–298.3 nM) was significantly higher than that of the normal-Ig-E group (mean, 65.73 nM; 18.18–139.8 nM; $P<0.05$; Fig. 1). All dogs with adverse drug reactions in the present study exhibited high blood histamine concentrations ($P<0.05$; Table 4).

DISCUSSION

Although anaphylaxis may develop at any time during general anesthesia, in 90% of cases in humans, anaphylaxis occurs upon induction of anesthesia [13]. In dogs, the use of propofol as an injectable drug for anesthesia should be considered as posing the greatest risk of anaphylaxis. However, in the present study, dogs with high-IgE levels and anamnesis of allergy did not exhibit severe anaphylactic reactions—such as cardiopulmonary arrest or cardiovascular collapse—to propofol administration. This result suggests that propofol might be a relatively safe drug in the canine patient with high-IgE level.

In humans and dogs, IgE and histamine release is involved in the pathology of anaphylactic shock, promoting hypovolemia and distributive shock—as a result of decreased venous return because of peripheral venous dilation and extravasation of blood components—as well as mixed shock associated with depressed cardiac function and severe hypotension caused by reduced left-atrial filling volume due to bronchial spasm [1, 18, 26]. Humans are particularly prone to anaphylaxis induced by muscle relaxants (12–30%), and caution is required since bradycardia is more frequent than previously thought [18]. Adverse events suggestive of anaphylaxis in humans include mucocutaneous (systemic rashes, pruritis, flushing, edema and wheals), respiratory (dyspnea, airway stenosis/spasm, wheezing and hypoxemia) and circulatory (hypotension, impaired consciousness and symptoms associated with peripheral organ failure due to hypotension) symptoms, with hypotension being defined as less than 70% of normal blood pressure (particularly systolic pressure) [23, 27, 28]. Cutaneous signs, such as hives, pruritus or flushing, and perioral edema are evident in over 80% of cases of human anaphylaxis. Additionally, in over 50% of patients, circulatory symptoms (hypotension, circulatory collapse or cardiopulmonary arrest) are the initial symptoms on the basis of which anaphylaxis is confirmed [15, 16, 24]. In animals, should bronchial spasm leading to unexplained circulatory collapse or respiratory arrest occur during surgery, the surgical covering on the animal must be removed, and the fur parted to check the skin for cutaneous signs. In case of anaphylaxis caused by muscle relaxants or other agents in humans, cutaneous signs are often transient and frequently overlooked [5]. In case of more acute, serious anaphylactic reactions, circulatory collapse or respiratory arrest might occur prior to the appearance of cutaneous symptoms. Therefore, caution is required since the absence of mucocutaneous symptoms does not necessarily rule out the possibility of anaphylaxis completely [18]. According to Mitsuhata [18], tachycardia is a frequent occurrence during anaphylaxis in humans. However, given that bradycardia is more common than previously thought, we evaluated bradycardia in addition to hypotension and tachycardia in the present study.

Flushing was one of the adverse drug reactions observed in this study. However, definitive diagnosis of anaphylaxis on the basis

of flushing alone is challenging in the absence of more easily determined cutaneous manifestations, such as edema or wheals. Use of ventilators might delay the identification of anaphylaxis [23, 25, 27, 28]. In the present study, ventilation was managed by spontaneous respiration in all the animals, and, although respiratory depression is a known side effect of propofol in dogs [19], no instances of severe respiratory symptoms of anaphylaxis—such as dyspnea, airway stenosis/spasm, wheezing or hypoxemia—were observed. As for flushing, respiratory depression alone might not necessarily indicate anaphylaxis, and the possibility that it may have been mistakenly attributed to anaphylaxis cannot be ruled out. Nevertheless, the incidence of adverse drug reactions in the high-IgE group (21.4%) in the present study was higher than that in the normal-IgE group (14.3%).

Additionally, the mean plasma histamine concentration in the high-IgE group was significantly higher than that in the normal-IgE group. Tanaka *et al.* [29] reported mean blood histamine concentrations of 72.6 and 31.4 nM in dogs with mast cell tumors and control dogs, respectively; in comparison with the reference value of 72.6 nM, the blood histamine concentrations of all dogs with adverse drug reactions in the present study were high, with the mean histamine concentration of the high-IgE group being higher than that of the normal-IgE group, which makes it highly likely that the adverse drug reactions observed in the present study actually represented anaphylaxis.

Elevated plasma histamine concentrations indicate activation of mast cells and basophils, as demonstrated by the release of histamine into blood in IgE-mediated hypersensitive reactions to food antigens in dogs [8]. However, such activation is evident in both allergic and non-allergic mechanisms [18]. Even in the absence of elevated blood histamine concentrations, immune and non-immune mechanisms cannot be ruled out [18]. In humans, atopic dermatitis may occur without the involvement of IgE, through upregulation of cytokine production (interleukin-18 and interferon-γ) even in the absence of a Th2 immune response [12, 32]. Mast cells possess various receptors, including those for complement factors (C3a and C5a), lectins, osmolality and substance P, which serve to increase blood histamine concentrations through degranulation in a manner similar to that of IgE antigens [9]. In the present study, one of the dogs in the normal-IgE group exhibited a high plasma histamine concentration, which was attributed to a reaction not mediated by IgE, as described above. Thus, anaphylaxis cannot be definitively diagnosed on the basis of plasma histamine concentrations alone. However, in the present study, the overall plasma histamine concentrations differed significantly between the high- and normal-IgE groups, and, in most cases, a high value might be of supplementary value in the diagnosis of anaphylaxis.

However, since definitive diagnosis of anaphylaxis on the basis of plasma histamine concentrations alone is challenging, further tests must be considered. Other tests used in humans include quantitative analysis of tryptase, a neutral protease present in mast cell granules, and the leukocyte histamine-release test [5, 14]. Since securing of the airway took precedence over perioperative sampling in the present study, giving rise to issues related to the timing of blood sample collection, it is necessary to consider tests that can be performed over longer periods, such as urinalysis for N-methylhistamine, a histamine metabolite measurable for 24 hr after the onset of anaphylaxis, or β-tryptase, which can be measured using samples frozen for a year at −20°C [15]. In dogs, histamine-release measurements after calcium ionophore stimulation are positively correlated with mast cell count in peripheral blood. Therefore, we intend to investigate the possibility that peripheral blood mast cell count, which can be easily performed at the bedside, might also be useful for diagnosis of anaphylaxis [29].

In humans with a history of drug-induced allergy not limited to propofol, particular caution is required during the first 2–3 min after propofol administration, when anaphylaxis is most likely to occur, and a posture of readiness must be adopted during this period [14, 30]. Among human patients who develop propofol-induced anaphylaxis, 64% have a history of some sort of allergy [14]. Therefore, preoperative testing, preparedness for the eventuality of anaphylaxis, and careful anesthetic administration are necessary during propofol administration in dogs with allergies or a history of anaphylaxis. However, in a study involving 28 children with IgE-type immediate allergy, including one with a history of egg-induced anaphylaxis, only one child with no history of anaphylaxis exhibited erythema and hives upon propofol administration; the authors, therefore, concluded that propofol is safe to use in children with egg allergy but without a history of anaphylaxis [20]. In this previous study, 43% of patients were allergic to peanuts, which cross-reacts with soy proteins; the authors concluded from their results that propofol might be relatively safe even for patients with soy allergy [20].

Despite the fact that 92.9% of the dogs in the high-IgE group had a history of allergy, the incidence of adverse drug reactions in the present study was low (21.4%). All instances of adverse reactions were mild, and there was no case of severe anaphylaxis. These findings suggest that the use of propofol might be relatively safe even in dogs with a history of allergy as well as in those with high concentrations of egg white/chicken or soy IgE, provided that anesthesia is carefully monitored during the perioperative period and a posture of preparedness is adopted.

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