

Evidence-based guidelines for anti-allergic drug withdrawal times before allergen-specific intradermal and IgE serological tests in dogs

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Background – Anti-allergic drugs (e.g. antihistamines, glucocorticoids and ciclosporin) are often administered to dogs with atopic dermatitis to relieve pruritus and skin lesions. Allergen-specific intradermal tests (IDT) and allergen-specific IgE serological (ASIS) tests are used to characterize the allergens to which dogs are hypersensitive. Anti-allergic drugs have the potential to influence the results or interpretation of these tests.

Objectives – To provide evidence-based recommendations for anti-allergic drug withdrawal times before IDT and ASIS tests.

Methods – Three citation databases and abstracts from international meetings were searched for relevant studies. Studies were grouped based on similar interventions and types of tests. Withdrawal times for each type of drug and test were then extrapolated from the study results.

Results – Before the assessment of immediate reactions to IDT, proposed optimal withdrawal times for antihistamines, oral glucocorticoids, topical/otic glucocorticoids and ciclosporin are 7, 14, 14 and 0 days, respectively. Studies have provided no evidence for drug withdrawal prior to ASIS tests for oral ciclosporin or prednisone/prednisolone. Owing to a lack of studies, recommendations for withdrawal times before ASIS tests cannot be made for topical glucocorticoids and antihistamines.

Conclusions and clinical importance – These proposed withdrawal times are based on the existing evidence at the end of 2011. Care must be taken before extrapolating the suggested withdrawal times to other species, higher dosages, different formulations and/or durations of administration of tested drugs, as well as to other medications from the same category.

Introduction

Canine atopic dermatitis (AD) is currently defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features, which is most commonly associated with the presence of IgE antibodies directed against environmental allergens.¹ Based on this definition and clinical experience, it is now accepted that dogs with AD are hypersensitive to environmental allergens, to food allergens (i.e. food-induced AD) or to both types of allergens.^{1–3}

Allergen-specific intradermal tests (IDT) and IgE serological (ASIS) tests are used to test for the presence of

IgE-mediated sensitization to environmental allergens in dogs with AD.⁴ These tests are most commonly performed with the aim of identifying relevant nonfood allergens and to institute allergen-specific immunotherapy.^{4,5} Given that many dogs with AD receive anti-inflammatory and antipruritic medications that could influence the results or interpretation of these tests, variable drug withdrawal times are usually advocated.^{4,5} Currently, these withdrawal times have historically been based more often on tradition and clinical impressions rather than on scientific evidence.

The aim of this review was to provide recommendations for anti-allergic and anti-inflammatory drug withdrawal times before IDT and ASIS tests based on the best evidence existing at the end of 2011.

Methods

Identification of existing evidence

The authors searched for relevant studies by querying three internet databases (MEDLINE via PubMed, Thomson Reuters' Web of Science and CAB Abstract via EBSCO Host) for articles published between 1 January 1985 and 31 December 2011.

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The following disease- and species-restricted search strategy was used: (i) dog or dogs or canine; (ii) atop* or allerg*; (iii) skin or intra-dermal or *vitro* or serolog* or IgE; (iv) human or child*; and (v) #1 AND #2 AND #3 NOT #4.

To identify studies solely presented in abstract form, the authors either hand-searched congress proceedings or screened online published abstracts from the three leading international veterinary dermatology congresses, namely the World Congresses of Veterinary Dermatology (first to sixth), the annual joint congresses of the European Society of Veterinary Dermatology (ESVD) and European College of Veterinary Dermatology (ECVD), as well as those of the North American Veterinary Dermatology Forum [previously Annual Meeting of the American Academy of Veterinary Dermatology (AAVD) and American College of Veterinary Dermatology (ACVD)]. Abstracts were searched for congresses held between 1985 and 2011.

Determination of withdrawal times

All abstracts were screened for applicable material, and studies were selected when relevant to the subject of this review. After reviewing the available evidence, studies were grouped based on testing method (IDT or ASIS) and drug category.

The results of each study were summarized, and the following two parameters were then proposed for each drug category.

- 1 'Optimal withdrawal times' (OWTs) are those that have been shown, or are very likely based on mechanism of action, to be associated with no drug interference on test results.
- 2 'Minimal withdrawal times' (MWTs), which are shorter than OWTs, are defined as those that might, at most, be associated with a small inhibitory effect that should not affect the interpretation of most test results.

Results

Allergen-specific intradermal testing

Effect of oral antihistamines

There are three studies that have examined the influence of oral antihistamines on IDT results.

In one study,⁶ 18 dogs with previously positive IDT reactions to flea allergens were treated with hydroxyzine hydrochloride (manufacturer not specified) at 3 mg/kg twice daily orally (p.o.) for 1 or 4 weeks. Intradermal (i.d.)

injections of histamine and flea allergens yielded reactions that returned to normal or near normal levels by 5 days after drug cessation. There were no noticeable differences in recovery of IDT reactivity between 1 and 4 weeks of hydroxyzine administration.⁶

In another study,⁷ six normal laboratory dogs were given a single dose of 2 mg/kg hydroxyzine pamoate (PCCA, Houston, TX, USA). After 24 h, the inhibition of histamine reactivity was about 40% compared with baseline and half of the maximal inhibition. Extrapolation of the inhibition curve suggested that, by 36 h after drug administration, histamine reactivity would no longer be inhibited.⁷

Finally, 10 house dust mite (HDM)-reactive dogs were treated with cetirizine (Zyrtec; UCB Pharma, Madrid, Spain) at 1 mg/kg once daily p.o. for 7 days.⁸ At the end of the 1 week treatment period, IDT reactions to HDM and histamine were inhibited by an average of 49 and 36%, respectively. Reactions had returned to normal values within 7 days of discontinuing cetirizine.⁸

In summary, the results of the two studies performed in dogs with spontaneous hypersensitivity suggest that, by 1 week after oral antihistamine discontinuation, the interpretation of IDT results would be similar, or closely similar, to that done before drug initiation,^{6,8} the OWT was therefore set at 7 days (Table 1). In cases where such delay cannot be considered, the results from the study by Bizikova *et al.* suggest that 2 days may be a suitable MWT.⁷ It is important to keep in mind that such withdrawal times are likely to vary with the type of antihistamine used and its dose, frequency and, perhaps, duration of administration.

Effect of short-acting oral glucocorticoids

Results from five studies are relevant to the evaluation of the effect of oral glucocorticoids on IDT reactivity.

In the first study, 10 beagles experimentally sensitized to fleas received either 0.55 mg/kg of prednisone (Sigma Chemical Company, St Louis, MO, USA) or placebo twice daily for 5.5 days.⁹ Prednisone treatment led to a

Table 1. Summary of optimal and minimal withdrawal times before intradermal and serological tests in dogs

	Drug example	Optimal withdrawal times (days)	Minimal withdrawal times (days)
Intradermal tests*			
Antihistamines (oral)	Hydroxyzine, cetirizine	7	2
Glucocorticoids (short-acting oral)	Prednisone, prednisolone	14	Unknown
Glucocorticoids (long-acting injectable)	Methylprednisolone acetate	Unknown	28
Glucocorticoids (topical)	Hydrocortisone, triamcinolone	14 (strong potency)	0 (weak potency)
Glucocorticoids (otic)	Betamethasone, mometasone	14	0
Ciclosporin (oral)	Ciclosporin	0	0
Tacrolimus (topical)	Tacrolimus	0	0
Pentoxifylline (oral)	Pentoxifylline	0	0
Ketoconazole (oral)	Ketoconazole	0	0
Essential fatty acids (oral)	Essential fatty acids (various)	0	0
IgE serological tests			
Antihistamines (oral)	Not tested	Unknown	0
Glucocorticoids (short-acting oral)	Prednisone, prednisolone	0	0
Glucocorticoids (long-acting injectable)	Methylprednisolone acetate	<28	Unknown
Glucocorticoids (topical or otic)	Not tested	Unknown	0
Ciclosporin (oral)	Ciclosporin	0	0

*For intradermal tests, withdrawal times mentioned are those for the evaluation of immediate-phase reactions; for details on late-phase reactions, please refer to the text.

statistically significant reduction in immediate wheal diameter after injection of flea allergen compared with baseline values, but the average difference at the end of the treatment (<2 mm) would be unlikely to have affected the interpretation of the test. This lack of clinically relevant effect was corroborated by the lack of statistically significant differences in subjective scores during this intervention.⁹ In contrast, there was a statistically and clinically significant inhibitory effect of prednisone on the objective and subjective assessment of 24 h late-phase reactions during the study.⁹

In a second study,¹⁰ the IDT reactivity to flea antigen was not significantly different, compared with baseline values, after treatment with prednisone (manufacturer not specified) at 0.5 mg/kg twice daily for 7 days, then once daily for 7 days and then every other day for 14 days. In contrast, treatment with prednisone at 1 mg/kg once daily for 4–6 weeks significantly reduced IDT reactivity to histamine and pollen allergens in experimentally sensitized dogs.¹⁰

In a third study,¹¹ eight beagles with flea-allergic dermatitis were treated with prednisolone (manufacturer not specified) at 1 mg/kg/day for 8 weeks. Treatment for 5 weeks did not significantly affect IDT immediate reactivity to the major flea salivary allergen, Cte f 1.¹¹

Furthermore, the administration of prednisolone (manufacturer not specified) at 0.5 mg/kg twice daily for 3 days to five laboratory dogs did not seem to affect immediate skin test reactivity to anti-IgE antibodies.¹² However, at the same time, there were no macroscopically evident late-phase reactions in prednisolone-treated dogs, in contrast to the untreated dogs.¹²

Finally, 10 HDM-reactive dogs were treated with oral prednisolone (Deltacortril; Pfizer, Istanbul, Turkey) at 1 mg/kg once daily for 3 days, then 0.5 mg/kg once daily for 2 days and then 0.25 mg/kg once daily for 2 days.⁸ After 1 week of treatment, IDT reactions to HDM and histamine were inhibited by an average of 51 and 31%, respectively.⁸ Seven days after discontinuation of prednisolone (i.e. study day 14), the surface of IDT reactions had increased markedly compared with the immediate post-treatment values, but HDM and histamine reactions were still significantly lower than at baseline.⁸

In summary, these studies provide conflicting results, implying either a lack of effect on^{10–12} or an inhibition of^{8–10} immediate IDT reactivity by oral glucocorticoids in dogs. There was, however, a clearer inhibitory effect on IgE-mediated late-phase reaction.^{9,12} Based on the available evidence suggesting a rapid increase in histamine and allergen wheal diameter after prednisolone discontinuation,⁸ the OWT should be longer than 7 days. Given a precautionary approach, an OWT of 14 days is proposed, while an MWT cannot be estimated with certainty (Table 1). As a dosage- and time-dependent inhibitory effect on IDT reactivity is suggested by one study,¹⁰ this factor must be taken into account before extrapolating these withdrawal times to other glucocorticoid dosages and durations of administration.

Effect of long-acting injectable glucocorticoids

In a single study evaluating this type of intervention,¹³ methylprednisolone acetate (manufacturer not specified)

was given at 2 mg/kg subcutaneously (s.c.) twice, 1 month apart, to eight dogs with experimental flea-allergic dermatitis. One month after the second injection, there was an incomplete suppression of immediate IDT reactions to flea salivary allergens compared with reactions of untreated control dogs; further details were not available for review.¹³

In summary, insufficient data are available to generate a meaningful OWT; an MWT of at least 28 days is proposed (Table 1).

Effect of topical glucocorticoids

Four studies have tested the effect of different topical glucocorticoid formulations on IDT reactions in dogs.

In one study,¹⁴ 16 normal dogs were treated with a twice-weekly application of a 1% hydrocortisone leave-on conditioner (ResiCORT; Virbac, Fort Worth, TX, USA) or its vehicle for 6 weeks. Seven pruritic dogs were treated in a similar manner with the hydrocortisone conditioner. After 2, 4 and 6 weeks of this intervention, there was no significant reduction in immediate reactivity to i.d. injections of histamine.¹⁴

A vehicle-controlled blinded study tested the same conditioner, which was applied to the skin once daily for 3 days.¹⁵ Wheal diameters, but not erythematous flares, after anti-IgE i.d. injections were significantly lower after treatment with the 1% hydrocortisone conditioner than after its vehicle. However, the median decrease in diameter was only 2 mm, which would be unlikely to affect IDT interpretation. In contrast, there was no noted impact on the clinical evaluation of late-phase reactions.¹⁵

In another experiment,¹⁶ a 0.0584% hydrocortisone aceponate spray (Cortavance; Virbac, Carros, France) was applied to both axillae, the groin and one side of the thorax of 10 Maltese-beagle atopic dogs once daily for 14 days. After 7 and 14 days, there was a significant inhibition of immediate reactivity after i.d. injections of histamine and anti-IgE antibodies on the treated side of the thorax. Immediate IDT reactions were also reduced on the untreated side of the thorax after 14 days. Late-phase reactions after anti-IgE i.d. injections were significantly reduced on both treated and untreated sides of the thorax after 7 and 14 days. Normal to near normal immediate reactivity to histamine returned at untreated sites within 2 weeks of discontinuation of treatment.¹⁶

Finally, sprays containing either 0.015% triamcinolone (Genesis; Virbac, Fort Worth, TX, USA) or 1% hydrocortisone plus 1% pramoxine (Relief HC; Teva Animal Health, St Joseph, MO, USA) were applied once daily for 1 week to the axillae, groin and one side of the thorax of 10 Maltese-beagle atopic dogs.¹⁷ Immediate reactions to i.d. injections of histamine and anti-IgE antibodies were significantly decreased for at least 1 week post-treatment on the treated side of the thorax of dogs that received triamcinolone compared with those treated with hydrocortisone and pramoxine; there was no significant inhibition of IDT reactions on the untreated side of the thorax.¹⁷

In summary, the variability of the study designs and products used renders the determination of universal OWT and MWT difficult. Nevertheless, based on the evidence available from the testing of a potent topical glucocorticoid (Cortavance; Virbac, Carros, France),¹⁶ an OWT

of 14 days is proposed (Table 1). For lower-potency topical glucocorticoid formulations, an MWT of 0 days is likely to be possible.^{14,15,17}

Importantly, two studies have confirmed that a difference in IDT reactivity might occur between sites previously treated with a topical glucocorticoid and areas distant from application sites.^{16,17} This factor must be taken into consideration, and it is recommended that IDT be performed away from glucocorticoid application areas; how great that minimal distance should be is unknown.

Effect of otic glucocorticoids

Only two studies evaluated the influence of glucocorticoid-containing otic formulations on IDT results in dogs.

In the first study,¹⁸ eight dogs were treated with a 0.088% betamethasone-containing otic ointment (Otomax; MSD Animal Health, Carbalosa de la Sagrada, Spain) twice daily for 2 weeks. At the end of treatment, the immediate IDT reactivity to histamine and two of seven tested allergens was statistically significantly reduced compared with pretreatment values. However, the average reduction in IDT reaction diameters was less than 1 mm, and it is unlikely that this intervention would have affected IDT interpretation.¹⁸

In the second study,¹⁹ 20 dogs with AD were treated with a 0.1% mometasone furoate-containing otic suspension (Mometamax; Merck Animal Health, Summit, NJ, USA) once daily for 14 days. In three dogs, wheal scores after i.d. injections of histamine and anti-IgE antibodies were within 25% of pretreatment values 7 days after discontinuation of treatment. In all other dogs, wheal scores returned to similar levels within 14 days of drug withdrawal.¹⁹

In summary, both these studies established that the use of a glucocorticoid-containing otic formulation can significantly reduce IDT immediate-phase reactivity, but the magnitude of the reduction is unlikely to affect IDT interpretation greatly, unless, perhaps, reactions are borderline positive.^{18,19} While an OWT of 14 days might be necessary to eliminate any risk of drug interference, especially for weak reactions, an MWT of 0 days could be considered after verification of appropriate reactivity to positive controls (Table 1).

Effect of oral ciclosporin

Four studies tested the influence of oral ciclosporin on IDT in dogs.

In one study,²⁰ ciclosporin (Atopica; Novartis Animal Health, Basel, Switzerland) was administered at 5 mg/kg p.o. once daily for 6 weeks to six dogs with AD. There were no statistically significant differences in positive (i.e. moderate to strong) reactions to environmental allergens before and after treatment.²⁰

In a second study, eight beagles with flea-allergic dermatitis were treated with ciclosporin (Neoral; Novartis, Basel, Switzerland) at 5 mg/kg p.o. once daily for 8 weeks.¹¹ After 5 weeks, ciclosporin had not significantly altered the IDT immediate reactivity to Cte f 1, the major flea allergen.¹¹

In another trial, 16 dogs with AD were randomly given either placebo or ciclosporin (Atopica; Novartis Animal

Health, Basel, Switzerland) for 30 days at 5 mg/kg once daily.²¹ Similar to the results of the other trials,^{11,20} ciclosporin did not significantly inhibit IDT immediate reactivity to the tested allergens compared with placebo.²¹

In contrast to these three studies, ciclosporin (Neoral; Novartis, Basel, Switzerland) given at the same dosage (5 mg/kg once daily) to four laboratory dogs for 30 days was found to attenuate significantly IDT immediate reactivity to *Ascaris* allergen, and the reduction in reactivity was correlated with lower levels of histamine amounts collected by dermal microdialysis.²²

In summary, while one experimental study found some inhibitory effect of ciclosporin on the IDT result for one allergen,²² three studies including dogs with spontaneous AD found no such inhibition.^{11,20,21} As a result, a withdrawal of short-term (i.e. 6–8 weeks) ciclosporin is probably not needed prior to IDT (Table 1).

Effect of topical tacrolimus

A 0.1% tacrolimus ointment (Protopic; Astellas Pharma, Northbrook, IL, USA) was applied to the lesional skin of nine house dust- or HDM-sensitive dogs with AD once daily for 4 weeks.²³ After 4 weeks of tacrolimus, immediate IDT reactions to histamine, allergens or lipopolysaccharide were not significantly different from baseline values. In contrast, some of the late-phase reactions to allergens were significantly reduced by tacrolimus. Late-phase reactions took up to 4 weeks to return to pretreatment values, but by 2 weeks after discontinuation of treatment, the 4 h reaction to house dust as well as the 4 and 6 h late-phase reactions to HDM had returned to normal.²³

In summary, topical tacrolimus does not appear to interfere with immediate IDT reactions performed outside of the treatment area; however, late-phase reactions might be affected. Withdrawal times of 0 days for immediate IDT reaction evaluation and 14 days for late-phase reaction grading are proposed (Table 1).

Effect of oral pentoxifylline

Ten HDM-hypersensitive atopic dogs were treated with oral placebo or pentoxifylline (Trental; Hoechst-Roussel Pharmaceuticals, Trenton, NJ, USA) at 10 mg/kg twice daily for 4 weeks.²⁴ After treatment with pentoxifylline, there was no significant inhibition of immediate IDT reactions to HDM allergens compared with baseline values.²⁴ In contrast, late-phase reactions to lipopolysaccharide were significantly decreased in comparison to pretreatment and placebo scores.²⁴

In summary, as pentoxifylline, at low dosages, does not appear to interfere with the immediate IDT reaction to environmental allergens,²⁴ a withdrawal of pentoxifylline is not needed prior to IDT (Table 1). Late-phase reactions are likely to be altered by pentoxifylline therapy, but specific withdrawal times for such reactions could not be assessed.

Effect of oral ketoconazole

Twelve HDM-sensitized dogs with AD received ketoconazole (Nizoral; Janssen, Titusville, NJ, USA) at 5 mg/kg twice daily for 3 weeks.²⁵ Treatment with ketoconazole

did not affect immediate IDT reactivity to histamine or HDM allergens.²⁵

In summary, because of the lack of detected interference of ketoconazole on the immediate IDT reaction to HDM allergens and histamine,²⁵ a withdrawal of ketoconazole is not needed before IDT (Table 1).

Effect of oral essential fatty acids

Two fatty acid supplements (Efavet Regular or HGF; Efamol Vet, Guildford, UK; now MSD Animal Health, Milton Keynes, UK), were given for up to 118 weeks to 20 dogs with AD.²⁶ Overall, treatment with these fatty acid supplements did not alter the immediate IDT reactivity to histamine.²⁶ There was an occasional reduction in average wheal diameter after the injection of some allergens, but this change would have been unlikely to have affected the interpretation of IDT results.²⁶

In summary, there are numerous formulations of essential fatty acids available for animal use, but only one study evaluated whether these supplements would affect immediate IDT reactivity.²⁶ As this study did not report any difference in immediate IDT results during fatty acid supplementation, a withdrawal of fatty acids prior to the performance of IDT does not appear to be needed (Table 1).

Allergen-specific IgE serological testing

Effect of oral antihistamines

The effect of type 1 antihistamines on ASIS has not been studied in dogs. However, the antagonism of the type 1 histamine receptor by antihistamines should not, at least in theory, interfere with the measurement of allergen-specific IgE in the patient's serum.²⁷ As a result, a withdrawal of antihistamines before ASIS is theoretically not needed, but this assertion remains unproven.

Effect of short-acting oral glucocorticoids

There are two studies that have tested the influence of oral glucocorticoid on IgE serological tests.

In one study,²⁸ prednisolone or prednisone (manufacturer not specified) was administered to 15 dogs with AD at 1.1 mg/kg once daily for 1 week and then every other day for 2 weeks. Overall, this had no effect on the interpretation of the ASIS results (Bioproducts DVM, Inc., Tempe, AZ, USA).²⁸

In a second study described in the preceding IDT section,¹¹ prednisolone was administered to eight dogs with flea-allergic dermatitis at 1 mg/kg/day for 8 weeks. After 5 and 7 weeks of treatment, there were no significant differences in Cte f 1-specific IgE serum levels (Heska Corporation, Loveland, CO, USA) compared with baseline values.¹¹

In summary, based on the limited data available for review,^{11,28} oral glucocorticoids given at anti-allergic dosages for less than 2 months are unlikely to have an effect on IgE serological tests (Table 1). A withdrawal time of 0 days is proposed.

Effect of long-acting injectable glucocorticoids

In one study already described in the IDT section above,¹³ eight dogs with experimental flea-allergic dermatitis were

treated with methylprednisolone acetate (manufacturer not specified) at 2 mg/kg s.c. twice, 1 month apart. One month after the second injection, there was no reported inhibition of serum levels of IgE specific for flea salivary allergens (Heska Corporation).¹³

In summary, insufficient data are available to estimate an accurate OWT, but study results suggest that it may be less than 28 days (Table 1).

Effect of topical and otic glucocorticoids

The effect of topical and otic glucocorticoid formulations on ASIS has not been tested in dogs. However, as prednisolone given p.o. for 7 weeks did not affect IgE serological test results,¹¹ it is unlikely that topical or otic glucocorticoids would do so either. Consequently, an MWT of 0 days is proposed.

Effect of oral ciclosporin

Three studies evaluated the influence of oral ciclosporin on the results of ASIS.

In the first study,¹¹ eight beagles with experimental flea-allergic dermatitis received ciclosporin (Neoral; Novartis, Basel, Switzerland) at 5 mg/kg/day once daily for 8 weeks. After 5 and 7 weeks of treatment, there were no reported relevant changes in Cte f 1-specific IgE serum levels (Heska Corporation).

In a second study,²¹ ciclosporin (Atopica; Novartis Animal Health, Basel, Switzerland) was administered to 16 dogs with AD for 30 days at 5 mg/kg once daily. This regimen did not significantly alter ASIS results (Heska Corporation).²¹

Finally, ciclosporin (Neoral; Novartis, Basel, Switzerland) was given at the same dosage (5 mg/kg once daily) to four laboratory dogs for 30 days.²² This regimen did not result in a significant change in the dogs' total IgE serum levels determined using a research laboratory ELISA (Bethyl Laboratories, Montgomery, TX, USA).²²

In summary, based on this evidence,^{11,21,22} ciclosporin given for up to 2 months at dosages used for the treatment of canine AD does not appear to affect the interpretation of ASIS results. As a result, a 0 day OWT is proposed (Table 1).

Discussion

In this review, we proposed two separate withdrawal times (OWT and MWT) for different categories of drugs for two types of tests (IDT and ASIS). These withdrawal times were determined based on the review and logical interpretation of the best evidence available at the time of writing.

Ideally, clinicians should test their patients beyond one of the proposed OWTs for the relevant drug and test of interest. In cases where this cannot be achieved because skin lesions and/or pruritus are too severe to permit a lengthy discontinuation of anti-allergic drugs before testing, veterinarians should perform the desired test between an MWT and an OWT.

To ensure that the IDT would still yield interpretable results if performed after an MWT, but before an OWT, clinicians should first assess the characteristics of the

immediate reactions at the positive control injection site. If the reactions appear smaller, less turgescient and/or less erythematous than normal, then the full IDT should ideally be repeated after the OWT for the drug of interest.

It is worth noting that the positive control used most widely, histamine at 1:100,000 (or 0.001%),⁵ assesses only the vasodilatation and increase in paracellular permeability of endothelial cells after binding of histamine to the type 1 histamine receptor. Histamine injections lead to congestion and plasma extravasation in the interstitial dermis and cause the typical macroscopic wheal-and-flare urticaria reactions.²⁹ Unfortunately, drugs that interfere with mast cell numbers and/or mast cell degranulation, but not with the histamine receptor and/or endothelial cell functionality themselves (e.g. high-dose ciclosporin and cromoglycate), would not be expected to affect immediate reactions that occur after histamine i.d. injections. In contrast, these drugs would be likely to reduce histamine release after allergen cross-linking of IgE on the surface of dermal mast cells, as occurs during an IDT with allergens to which a dog is hypersensitive. As a result of this phenomenon, a drug would be thought to not have interfered with the IDT (as assessed by a clear wheal at the histamine positive control site) when, in fact, it could have reduced mast cell histamine release and led to false-negative reactions at relevant allergen injection sites. For this reason, the addition of a second positive control that triggers mast cell degranulation (e.g. anti-IgE antibodies,³⁰ compound 48/80,³¹ codeine phosphate,³¹ concanavalin-A,³² calcium ionophore³² or substance P³²) might be worth considering.

A possible limitation of this review is that the reactivity to histamine, but not to environmental allergens, was used mainly to determine some of the withdrawal times in most studies. However, even if studies evaluating histamine reactivity were disregarded, the only difference in the proposed withdrawal times before IDT would be that the MWT after oral antihistamine administration would increase from 2 to 5 days.

The main drawback of this review is that the evaluated studies enabled the estimation of withdrawal times only for specific drugs, dosages, frequencies and lengths of administration. It is logical to expect that more potent drugs, as well as higher daily dosages and/or longer durations of administration might lead to different OWTs. Clinicians must consider these parameters before extrapolating the proposed withdrawal times to regimens different from those reported herein. Of note is that the withdrawal times discussed apply only to dogs with AD, but not to cats or horses with hypersensitivity dermatitis. Whether these recommendations can be extrapolated to these two other animal species in which hypersensitivity tests are commonly performed is unknown.

Finally, another possibly important weakness of this review is that the proposed withdrawal times were established based on data obtained from repeated IDT and ASIS with the implicit assumption that there would have been very little variability from test to test except for the sole effect of the evaluated drug. In fact, a recent study³³ showed that the intra-observer repeatability of IDT is only fair to moderate. As a result, it is possible that some of the mild inhibitory effects attributed to any of the tested

drugs might have been due simply to the low intra-observer repeatability of IDT. In contrast, for the three laboratories for which the repeatability and reproducibility of ASIS test results have been published based upon the use of internal quality controls (i.e. macELISA, Greer Laboratories, Lenoir, NC, USA;^{34–36} Allercept, Heska Corporation, Loveland, CO, USA;³⁷ and quantitative ELISA, Animal Allergy Clinical Laboratories, Inc, Sagamiara, Kanagawa, Japan³⁸) the consistency of ASIS results is generally considered acceptable. Thus, the issue of IgE serological test variability should be less of a concern if withdrawal studies are performed using ASIS performed in one of these laboratories.

This review highlighted the need for additional studies to test the effect of common drug interventions on IDT and ASIS. For example, there is a need to evaluate the effect of newer antihistamines, such as loratadine or fexofenadine, which have been used in dogs with AD.^{39,40} Likewise, in spite of its widespread use for many years, the effect of the antihistamine–glucocorticoid formulation that contains trimeprazine and low-dose prednisolone (Temaril P; Pfizer Animal Health, New York, NY, USA) has never been reported on IDT or ASIS. Other drugs that would need evaluation for test interference are the antidepressants that are sometimes used in pruritic dogs with AD (e.g. doxepin, fluoxetine and clomipramine).

Furthermore, to yield information on optimal drug withdrawal times that would be relevant to variable situations encountered in clinical practice, for example for oral glucocorticoids, it is recommended that tests be repeated after variable durations of drug administration (e.g. 1 day and 1, 2 and 4 weeks or longer). Likewise, for drugs used in practice at different dosages, inhibitory effects on test results should be evaluated with each dosage. After treatment is discontinued, tests should ideally be repeated after multiple drug discontinuation times (e.g. 1, 3, 5 and 7 days and weekly thereafter) so that the shortest withdrawal times could be determined precisely.

It is hoped that, in the future, manufacturers of newly approved drugs for treatment of canine AD would consider the evaluation of the inhibition of their drug on the tests discussed above. Studies to test the influence of anti-allergic drugs on oral food-provocation tests are lacking and clearly needed.

In summary, this review of existing evidence provides the basis for rational guidelines for withdrawal of anti-allergic drugs before the performance of IDT and ASIS tests. Clinicians using these tests are encouraged to test their patients beyond the OWTs proposed in Table 1. In cases where drugs cannot be discontinued because of quality-of-life concerns, the tests should be performed after an MWT, or the dogs should be given a drug with minimal effect on test results (e.g. ciclosporin). In the case of IDT, the reactivity to positive controls must first be judged to be adequate before the full test is performed.

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Résumé

Contexte – Les molécules anti-allergiques (ex. les antihistaminiques, les glucocorticoïdes et la ciclosporine) sont souvent administrées aux chiens atteints de dermatite atopique afin de réduire le prurit et les lésions cutanées. Les intradermoréactions (IDT) et les tests sérologiques IgE-spécifiques d'allergènes (ASIS) sont utilisés pour caractériser les allergènes auxquels les chiens sont sensibilisés. Les molécules anti-allergiques ont le potentiel d'influencer les résultats ou l'interprétation de ces tests.

Objectifs – Fournir des recommandations pour la durée d'éviction des molécules anti-allergiques avant les tests IDT ou ASIS.

Méthodes – Trois bases de données de référence et des résumés de conférences internationales ont permis de sélectionner les études les plus pertinentes. Les études ont été groupées selon les interventions semblables et les types de tests. Les temps d'éviction de chaque type de médicament et les tests ont été ensuite extrapolés des résultats.

Résultats – Avant l'évaluation des réactions immédiates aux IDT, les temps optimaux d'éviction proposés pour les antihistaminiques, les glucocorticoïdes oraux, les glucocorticoïdes topiques/auriculaires et la ciclosporine sont respectivement de 7, 14, 14 et 0 jours. Les études n'ont fourni aucune preuve d'éviction de traitement avant les tests ASIS pour la ciclosporine ou la prednisone/prednisolone orales. Faute d'études, aucune recommandation ne peut être faite pour l'éviction médicamenteuse avant les tests ASIS pour les corticoïdes oraux et les antihistaminiques.

Conclusions et importance clinique – Ces temps d'éviction proposés sont basés sur les preuves existantes fin 2011. Une attention particulière sera portée avant toute extrapolation de ces temps d'éviction à d'autres espèces, à des dosages plus élevés, des formulations différentes et/ou la durée d'administration des traitements testés ainsi qu'aux autres traitements de la même catégorie.

Resumen

Introducción – los fármacos antialérgicos (esto es, antihistamínicos, glucocorticoides y ciclosporina) se administran con frecuencia a perros con dermatitis atópica para aliviar el prurito y mejorar las lesiones de la piel. Las pruebas intradérmicas específicas de alérgenos (IDT) y las pruebas serológicas de IgE específica de alérgeno (ASIS) se utilizan para caracterizar los alérgenos a los cuales los perros tienen hipersensibilidad. Los fármacos antialérgicos podrían potencialmente influir los resultados o la interpretación de estas pruebas.

Objetivos – aportar recomendaciones basadas en evidencias para la interrupción del tratamiento antialérgico antes de las pruebas IDT y ASIS.

Métodos – se hizo una búsqueda de estudios relevantes en tres bases de datos con citas y en resúmenes de conferencias internacionales. Los estudios se agruparon basados en intervenciones similares y en el tipo de prueba. El intervalo de interrupción del tratamiento para cada tipo de fármaco y prueba fue entonces extrapolado de los resultados del estudio.

Resultados – antes de la valoración de las reacciones inmediatas a la IDT, se propone un periodo de interrupción ideal del tratamiento para antihistamínicos, glucocorticoides orales, glucocorticoides tópicos/óticos y ciclosporina de 7, 14, 14 y 0 días, respectivamente. Los estudios no aportan evidencia para una interrupción del tratamiento antes de las pruebas ASIS durante el tratamiento con ciclosporina oral o prednisona/prednisolona. Debido a la falta de estudios, no se puede hacer ninguna recomendación para la interrupción del tratamiento antes de las pruebas ASIS durante el tratamiento con glucocorticoides tópicos y antihistamínicos.

Conclusiones e importancia clínica – los tiempos propuestos de interrupción del tratamiento se basan en evidencias existentes hasta el final del año 2011. Se debe tener precaución antes de extrapolar estos tiempos a otras especies, dosis más elevadas, diferentes formulaciones y/o duración de la administración de los fármacos probados, así como para otros medicamentos de la misma categoría.

Zusammenfassung

Hintergrund – Antiallergische Medikamente (z.B. Antihistamine, Glukokortikoide und Ciclosporin) werden Hunden mit atopischer Dermatitis häufig gegeben, um den Juckreiz und die Hautveränderungen zu verbessern. Allergen-spezifische Intradermaltests (IDT) und Allergen-spezifische IgE-Serologie (ASIS) werden verwendet, um die Allergene, auf die Hunde hypersensibel reagieren, zu charakterisieren. Antiallergische Medikamente können potentiell die Ergebnisse oder die Interpretation dieser Tests beeinflussen.

Ziele – Das Ziel dieser Studie war es, auf Evidenz basierende Empfehlungen für das Absetzen von antiallergischen Medikamenten vor der Durchführung von IDT und ASIS Tests auszusprechen.

Methoden – Drei Literatur-Datenbanken und die Abstracts von internationalen Treffen wurden auf relevante Studien durchgesehen. Die Studien wurden auf der Basis ähnlicher Interventionen und Typen von Tests zusammengefasst. Die Zeiten für das Absetzen eines jeden Wirkstofftyps und Tests wurden von den Studienergebnissen extrapoliert.

Ergebnisse – Vor der Beurteilung von Sofortreaktionen auf den IDT betrugen die vorgeschlagenen optimalen Absetzzeiten für Antihistamine, orale Glukokortikoide, topisch/otisch verwendete Glukokortikoide und Ciclosporin 7, 14, 14 bzw. 0 Tage. Es gibt keine Studien, die Evidenz liefern für das geeignete Absetzen von oralem Ciclosporin oder Prednison/Prednisolon vor den ASIS Tests. Aufgrund fehlender Studien können für topisch verwendete Glukokortikoide und Antihistamine keine Empfehlungen bezüglich der geeigneten Absetzzeiten vor der Durchführung von ASIS Tests ausgesprochen werden.

Schlussfolgerungen und klinische Bedeutung – Die vorgeschlagenen Absetzzeiten basieren auf der existierenden Evidenz bis Ende 2011. Vorsicht ist angesagt, wenn die vorgeschlagenen Absetzzeiten extrapoliert werden auf andere Spezies, höhere Dosierungen, unterschiedliche Formulierungen und/oder die Dauer der Verabreichung der getesteten Wirkstoffe, sowie auf andere Wirkstoffe derselben Kategorie.

摘要

背景 – 抗过敏药物（如抗组胺剂、糖皮质激素和环孢素）常用来管理犬异位性皮炎，解除瘙痒和皮肤病变。特异性过敏原皮内试验（IDT）和特异性IgE抗体血清学（ASIS）试验用于显示过敏犬过敏原。抗过敏药物可能影响这些试验的结果或判读。

目的 – 提供在IDT和ASIS试验前抗过敏药物推荐停药时间的证据基础。

方法 – 搜索三个引文数据库和国际会议摘要中的有关研究。研究基于类似的试验干预和类型进行分组。由研究结果推测每种类型药物和试验的停药时间。

结果 – IDT即时反应评估前，所推荐的抗组胺剂、口服糖皮质激素、局部/耳部糖皮质激素和环孢素的最佳停药时间分别是7、14、14和0天。研究没有提供ASIS试验口服环孢素或泼尼松/泼尼松龙前停药的证据。由于缺乏研究，ASIS试验前不能提供局部糖皮质激素和抗组胺剂推荐的停药时间。

结论和临床价值 – 这些推荐的停药时间是基于2011年底年前的证据。进行推断前必须注意其他种类、更高剂量、不同配方和/或试验药物管理期间建议的停药时间，同其他同类药物也一样。

要約

背景 – 抗アレルギー薬（例：抗ヒスタミン剤、グルココルチコイドやシクロスポリン）は、アトピー性皮膚炎の犬の痒みや症状の緩和のためにしばしば投与される。アレルギー特異的皮内反応（IDT）やアレルギー特異的IgE血清学的（ASIS）検査が過敏症を示すイヌのアレルゲンを特定するために利用されている。抗アレルギー薬はそれらの検査の解釈や結果に影響を与える可能性がある。

目的 – IDTやASIS検査前の抗アレルギー薬中止期間について、根拠に基づいた提案を示すこと。

方法 – 本研究に関連する報告について、3つの引用データベースと国際的な学会の要約を検索した。同じ種類の治療と検査項目のタイプに従い、群分けを行った。それぞれの検査項目における薬剤の休薬期間は研究結果から推定した。

結果 – IDTにおける即時反応の評価前に、抗ヒスタミン剤、経口グルココルチコイド、外用あるいは点耳用グルココルチコイドやシクロスポリンの休薬期間は7日、14日、14日、0日と提案した。本研究によりASIS検査前に経口シクロスポリンあるいはプレドニゾン/プレドニゾロンを休薬することにはエビデンスがないと考えられた。外用のグルココルチコイドや抗ヒスタミン剤をASIS前に休薬するかどうかは報告がないことから判定できなかった。

結論と臨床的な重要性 – これらの提案された休薬期間は2011年末までに存在したエビデンスに基づいている。推奨される休薬期間を推定する前に他の動物種、高用量、異なった剤型や検査される薬剤および同じカテゴリーに属する他の薬剤の投与継続期間に注意する必要がある。