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INTERNATIONAL JOURNAL

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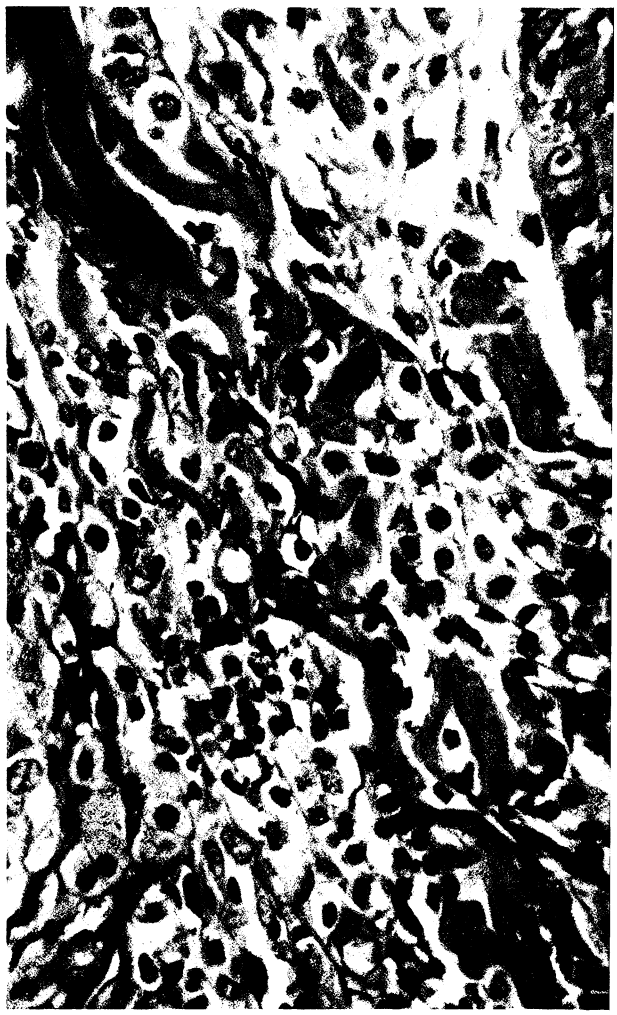
Veterinary Dermatology



IN THIS ISSUE

ISSN 0959 – 4493

PERGAMON PRESS

ord • New York • Seoul • Tokyo

Official Journal of the European Society of Veterinary Dermatology and the American College of Veterinary Dermatology

Published bimonthly in February, April, June, August, October and December by ESVD and ACVD.

Acknowledgements to abstract translators:
Dr. Victoria Holland (Spanish), Dr. Pascal Prélaud (French) and Dr. Elisabeth Venzl (Germany).

Annual Institutional Subscription Rates (1992): £130.00 (U.S.$199.50). Two-year institutional rate (1992/93): £247.00 (U.S.$399.10). Sterling prices are definitive. U.S. dollar prices are quoted for convenience only, and are subject to exchange rate fluctuation. Prices include postage and insurance and are subject to change without notice. There is a specially reduced rate of £60.00/$96.00 for individuals. Subscription rates for Japan include despatch by air and prices are available on application

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Members' subscriptions: Members of the European Society of Veterinary Dermatology and of the American College of Verterinary Dermatology are entitled to receive the Journal at a subsidised rate and should apply to their respective secretaries.

Publishing and Advertising Offices: Pergamon Press plc., Headington Hill Hall, Oxford OX3 0BW, U.K. and Pergamon Press Inc., 660 White Plains Road, Tarrytown, New York 10591/5153, U.S.A.

Typeset by Datapage Int., Dublin. Printed and bound by Pensord Press. Produced by David Parkes.

Veterinary Dermatology

Volume 2, (3/4), 1991

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ISSN 0959-4493

Cover illustration: Normal (left) and abnormal (right) collagen fibres of the superficial dermis in a Siamese cat with a perforating dermatitis (Masson's trichrome stain). From Scott and Miller, page 173.

Veterinary Dermatology, Vol. 2, No. 3/4, pp. 119–123, 1991
Printed in Great Britain.

0959-4493/91 $5.00 + 0.00

The Effect of Tiletamine-Zolazepam Anesthesia on the Response to Intradermally Injected Histamine in Cats

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Veterinary Dermatology 1991: 2: 119–123

Abstract—The purpose of this study was to evaluate the effect of intravenously administered tiletamine-zolazepam on the response of cats to intradermal injections of varying concentrations of histamine, thereby giving an indication of the feasibility of using tiletamine-zolazepam for the restraint of cats during intradermal skin testing.

Ten cats were injected intradermally with increasing concentrations of histamine and a negative control before and after anesthesia with tiletamine-zolazepam (5 $mg.kg^{-1}$ intravenously). The wheals produced by the eight different concentrations of histamine (1:100,000 to 1:9,600,000) and the negative control before and after anesthesia were compared in each cat. There was no significant difference in the response to the intradermal histamine injections before and after anesthesia. It was concluded that 4 $mg.kg^{-1}$ of tiletamine-zolazepame administered intravenously may be a good anesthetic choice for intradermal skin testing in cats.

Key Words: Intradermal skin testing; Cats; Tiletamine-zolazepam.

INTRODUCTION

Atopy (atopic dermatitis, allergic inhalant dermatitis) is a well recognized allergic skin disease in the dog (1, 2, 3). Affected individuals have an inherited predisposition to form IgE antibodies against environmental allergens and subsequently develop pruritic skin disease following re-exposure to these allergens. Canine atopy is classified as a type I hypersensitivity reaction where binding of allergens to mast cell fixed IgE or IgGd leads to degranulation and release of pharmacologically active compounds (1, 3, 4). A similar disease is recognized in humans (5, 6, 7).

The diagnosis of atopy in cats is based on intradermal skin testing and response to hyposensitization (9, 10, 11, 12). However, feline IgE has not been conclusively identified, even though a reaginic antibody was detected in cats with positive skin test reactions (8), which supports the premise that an IgE like antibody exists in cats.

Intradermal skin testing is the most commonly utilized procedure for the diagnosis of canine atopy (1). Physical restraint can be problematic and intradermal skin test results can be influenced by endogenous corticosteroid and/or epinephrine release in dogs (1, 2). Thus, immobilization with xylazine hydrochloride, tiletamine-zolazepam, short acting barbiturates or inhalation anesthesia has been recommended (2, 3, 13, 14, 15, 16).

Intradermal skin testing is not easily accomplished in the cat utilizing physical restraint alone. Movement can be expected, which may affect the quality of injections and influence the results of the skin test. Additionally, release of glucocorticoids and epinephrine would be expected to reduce skin test reactivity as reported in the dog (1, 2). Ketamine has been recommended as a satisfactory anesthetic for skin testing in cats (1, 2). Ketamine and diazepam in combination also have been used (17).

A new dissociative anesthetic product containing a 1:1 mixture by weight of tiletamine as dissociative and zolazepam as benzodiazepine, is approved as an injectable anesthetic agent for dogs and cats (Telazol, A. H. Robbins, Richmond, VA). Intravenous use produces effective chemical restraint for short diagnostic and minor surgical procedures (J. Ilkiw, Veterinary Medical Teaching Hospital, University of California, Personal communication, 1991).

Tiletamine-zolazepam anesthesia recently was reported by Codner to be a good choice for intradermal

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skin testing in the dog (13, 14). Diminution of skin test reactivity would be unlikely as tiletamine does not have antihistaminic action (18) and interaction of zolazepam and histamine has not been reported (14).

The purpose of this study was to evaluate the effect of intravenously administered tiletamine-zolazepam on the response of cats to intradermal injections of varying concentrations of histamine, thereby giving an indication of the feasibility of using tiletamine-zolazepam for the restraint of cats during intradermal skin testing.

MATERIALS AND METHODS

Eight female and three male domestic short haired cats from a colony of cats with a genetic predisposition to the development of feline eosinophilic granuloma at the University of California/Davis (19) were used in the study. On physical examination, all cats had normal haircoat and underlying skin. An indolent ulcer was present on the upper lip in one cat and ulcerations of the hard palate typical of eosinophilic granuloma were seen in two additional cats. A biopsy of these lesions confirmed the diagnosis (19). Ten cats had not received any topical or parenteral medication for at least two months prior to the study. The eleventh cat had completed a two-week-course of topical medication containing nystatin, neomycin sulfate, thiostreptone and triamcinolone acetonide (Panolog, Solvay Veterinary, Princeton, NJ) which was applied twice a day to an eosinophilic granuloma lesion in the preauricular region 14 days previously.

A protocol previously described was utilized (14). Skin testing was performed in all eleven cats on the left lateral thorax using only physical restraint. Skin testing was then repeated six hours later on the right lateral thorax utilizing tiletamine-zolazepam anesthesia.

An area of approximately 10×5 cm on the left lateral thorax of each cat was clipped with an electric clipper (Oster Clippers, Milwaukee, Wis.) using a No. 40 blade. Nine injection sites were marked with a permanent marker pen (Sharpie, Sanford Corp., Bellwood, IL.). One diluent control (Sterile diluent for allergenic extracts, buffered saline; Greer Laboratories, Lenoir, NC.). and eight diminishing dilutions of histamine (Histamine phosphate 2.75 mg/ml; Lily, Indianapolis, IN.) (1:100,000; 1:200,000; 1:400,000; 1:800,000; 1:1.600,000; 1:2,400,000; 1:4,800,000 and 1:9,600,000) were injected intradermally two cm apart in two horizontal rows. Only one injection of each dilution was made due to the size constraints of the thorax of cats and the increasing resistance of unanesthetized cats to the injection procedure. A volume of 0.05 ml was injected at each site using one milliliter tuberculin syringes and 26 gauge needles with intradermal bevels (Precision glide 26G 3/8 Becton Dickinson, Rutherford, NJ.). Fifteen minutes after injection, the wheals were graded from zero to four, based on size, elevation, erythema and induration (subjective evaluation). The diluent was used as a negative control and graded as zero, the most concentrated histamine dilution (1:100,000) served as a positive control and was classified as a four. The diameter of the wheals was measured in mm (objective evaluation).

Six hours later, each cat was administered 4 mg/kg tiletamine-zolazepam intravenously. The right lateral thorax was clipped in the corresponding area and the same procedure carried out as described above. Wheals were evaluated in a similar manner.

Subjectively graded responses to histamine injection at various dilutions before and after anethesia were compared using the nonparametric sign test for matched pairs. Objectively measured responses to histamine injection at various dilutions were compared using the paired T-test and the nonparametric Wilcoxin paired test for signed ranks. Hotelling's T square test was used to test the null hypothesis that all differences in mean wheal diameter were simultaneously zero. Linear and polynomial regression was used to see if differences in wheal diameter systematically varied with log histamine dilution. All analyses were performed using BMDP statistical software (20). Statistical adjustment for multiple comparisons to maintain a nominal level of significance of 0.05 was performed using the sequentially rejective multiple test procedure of Holm (20).

RESULTS

Tiletamine-zolazepam 4 $mg.kg^{-1}$ intravenously immobilized all cats for 20 to 40 minutes. Except for muscle tremors of the limbs, recovery was uneventful in all cats.

The median values of the subjective grading increased from zero to four without anesthesia and from zero to four with anesthesia as histamine concentration increased. Similarly, the mean diameter of the wheals increased in size from 4 to 11 mm and from 4.4 to 11.3 mm respectively (Table 1).

There was no significant difference between the mean wheal diameter values before and after anesthesia at each histamine solution. However, 12 of the 90 injection pairs showed a difference of more than one grade in the subjective evaluation and 21 injection sites varied more than three mm in wheal diameter.

The eleventh cat which received a corticosteroid-containing ointment two weeks prior to the study exhibited only a minimal response to all the intradermal injections including the most concentrated histamine dilution. Since it was probable that the previous therapy had suppressed skin test reactivity, this cat was not included in the statistical evaluation of the larger study.

All pairwise tests indicated that there was no significant difference ($p > 0.05$) in mean response to the intradermal injections before and after anesthesia.

Hotelling's T square test was not significant ($p > 0.05$), providing further evidence that the differences in mean wheal diameter at all dilutions were simultaneously zero. In addition, regression methods showed no evidence of a linear, quadratic, or cubic trend in the mean differences at different loghistamine dilutions.

DISCUSSION

Based on the result of this study, tiletamine-zolazepam appears to be an appropriate anesthetic for intradermal skin testing in cats. Four $mg.kg^{-1}$ tiletamine-zolazepam intravenously did not have a significant effect on wheal and flare response to intradermal injections of varying solutions of histamine.

As would be expected, the mean values of the subjective evaluation decreased with diminishing dilutions of histamine. the diameter of the wheals decreased similarly.

Feline atopy is believed to be a type I hypersensitivity. Thus, response to intradermal injections of histamine should produce wheal and flare reactions similar to those which allergens would produce in an atopic cat. The subjective grading from zero to four corresponds to currently employed grading responses to intradermally injected allergenic extracts in skin testing. The diluent serves as a negative control and histamine (1:100.000) as a positive control; the former being graded as zero, the latter as four.

Cats have thinner skin than dogs, thus, intradermal injections are more difficult to accomplish. Accidental subdermal injection is more likely to occur than in the dog. The variability in both the subjective (> 1 grade) and objective (> 3 mm) evaluation may in part be due to this.

In the subjective evaluation, a difference of more than one grade in the response to the intradermally injected histamine dilutions before and after anesthesia was noted twelve times. The reaction was more pronounced before anesthesia in six cases and after anesthesia in the other six.

Twenty-one of the 90 injection pairs showed a difference of more than three mm in the objective evaluation. Eight of these pairs were injections with either the negative control or the lowest histamine dilution, where one injection created a wheal and the other one did not. In ten of the 21 pairs, the wheal size was increased before anesthesia and in eleven of the pairs the wheal size was increased after anesthesia. Only one of the 21 varied more than one unit in the subjective gradings, which took into account not only size, but also the induration, elevation and erythema of the wheals.

Results seen in the eleventh cat show the possible influence of topical application of glucocorticoids on intradermal skin testing in cats. Topical absorption of glucocorticoids has been shown to produce adrenal suppression and iatrogenic hyperglucocorticoidism in dogs (21, 22, 23).

The cats in this study are part of a research colony and are habituated to handling and minor diagnostic procedures. Cats that are not commonly restrained could be expected to show substantially more resistance to the injections. Thus, it may be difficult to consistently inject the same amount of allergenic extract intradermally. Also, stress and subsequent endogenous release of epinephrine and corticosteroid may reduce dermal reactivity and thus interfere with skin test results.

Four $mg.kg^{-1}$ of tiletamine-zolazepam administered intravenously anesthesized all cats for a time period of between 20 and 40 minutes. This provides adequate time for the skin testing procedure and subsequent evaluating 15 minutes after the intradermal injections of the allergen extracts.

The dose of the anesthetic should be reduced in geriatric or debilitated cats and because the drug is excreted by the kidneys, in animals with impaired renal function. It is contraindicated in cats with pancreatic disorders and severe cardiac or pulmonary dysfunction (Package insert, Telazol, Animal Health Group, A. H. Robbins Company, Richmond, VA, 1978).

This study suggests, that tiletamine-zolazepam at $4\ mg.kg^{-1}$ IV may be a good anesthetic choice for intradermal skin testing in cats, since it did not interfere with the response to different dilutions of histamine intradermally. However, clinical trials are necessary to evaluate the influence of this anesthetic on the response to various intradermally injected allergenic extracts in atopic cats.

ACKNOWLEDGEMENTS

The authors thank Dr. Niels Pedersen for providing the cats. The technical assistance given by Ms. Nancy DeLemus was greatly appreciated.

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Résumé—Le but de cette étude était d'évaluer l'influence d'une injection intraveineuse de tilétamine-zolazepam sur la réponse de chats à des injections intradermiques de différentes concentration d'histamine, afin de savoir si une une anesthésie à l'aide de tilétamine-zolazepam était utilisable pour faire des tests cutanés chez le chat. Des concentrations croissantes d'histamine et un témoin négative ont été injectés par voie intradermique à dix chats avant et après injection IV de tilétamine-zolazepam (5 mg/kg). Le diamètre des papules aux neufs concentrations différentes d'histamine (1:100 000, 1:2 800 000, 1:4 800 000 et 1:9 600 000) et au témoin négatif ont été comparés pour chaque chat avant et après aesthésie. Il n'existait de différence significative avant et après anesthésie. Il a été conclu qu'une anesthésie à l'aide de 5 mg IV de tilétamine-zolazepam était utilisable pour effectuer des intradermoréactions chez le chat. [Mueller, R. S., Ihrke, P. J., Kass, P. H. Bettenay, S. V. The effect of tiletamine-zolazepam anesthesia on the response to intradermally injected histamine in cats (Etude de l'influence d'une anesthésie à l'aide de tilétamine-zolazepam sur la réponse à des injections intradermiques d'histamine chez le chat). *Veterinary Dermatology* 1991: 2: 119–123].

Zusammenfassung—Ziel dieser Studie war die Austwertung der Wirkung von intravenös verabreichtem Tiletamin-Zolazepam auf die Reaktion von Katzen gegenüber intradermal injiziertem Histamin unterschiedlicher Konzentrationen. So ergeben sich Hinweise auf die Eignung von Tiletamin-Zolazepan für die Ruhigstellung von Katzen bei intradermalen Hauttests. Bei zehn Katzen wurde Histamin in steigenden konzentrationen zusammen mit einer Negativkontrolle intradermal vor und nach Anästhesie mit Tiletamin-Zolazepam (5 mg/kg intravenös) injiziert. Bei jeder Katze wurden die Negativkontrollen und die lokalen Schwellungen durch die neun verschiedenen Histaminkonzentrationen (1:100,000–1:9,600,000) vor und nach der Anästhesic verglichen. Es ergaben sich keine signifikanten Unterschiedge in den Reaktionen auf intradermale Histamininjektionen vor und nach der Anästhesie. Daraus läßt sich schlußfolgern, daß 5 mg Tiletamin-Zolazepam, intravenös verabreicht, eine gute Anästhesiemöglichkeit für Hauttests bei Katzen darstellen. [Mueller, R. S., Ihrke, P. J., Kass, P. H., Bettenay, S. V. The effect of tiletamin-zolazepam anesthesia on the response to intradermally injected histamine in cats. (Die Wirkung einer Tiletamin-Zolazepam-Anästhesie auf die Reaktion gegenüber intradermal injiziertem Histamin bei Katzen). *Veterinary Dermatology*, 1991; 2: 119–123].

Resumen—El presente reportaje tiene como objetivo el estudio de la administración intravenosa de tiletamina-zolazepám en la respuesta de un grupo de gatos sometidos a la inyección intradérmica de diferentes concentraciones de histamina, dando asi una indicación de la utilidad de tiletamina-zolezopan para la inmobilización de gatos durante el test de la inyeccion intrdérmica. Se inyectaron intradermicamente diez gatos con concentraciones crecientes de histamina y un control negativo, antes y después de la anestesia producida con tiletamina-zolazepám (5 mg/kg de forma intravenosa). Luego se comparon las ronchas producidas por las diferentes concentraciones de histamina (1:100,000–1:9,600,000) y el control negativo, antes y después de la anestesia. No hubo diferencia significativa en la respuesta a la inyección intradérmica de histamina antes o después de la anestesia. Así, se concluyó que la administración de 5 mg de tiletamina-zolazepám de forma intravenosa podría ser un anestético satisfactorio en el test intradérmico llevado a cabo en gatos. [Mueller, R. S., Ihrke, P. J., Kass, P. H., Bettenay, S. V. The effect of tiletamine-zolazepam anesthesia on the response to intradermally injected histamine in cats (El efecto de la anestesia producida por tiletamina-zolezepám en la respuesta de gatos inyectados intradermicamente con histamina). *Veterinary Dermatology*, 1991; 2: 119–123].