



Retrospective review of diphenhydramine vs diphenhydramine plus glucocorticoid for the treatment of allergic reaction in cats

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Abstract

Objectives The aims of the present study were to report the outcomes of treating allergic reactions in cats with diphenhydramine vs diphenhydramine plus glucocorticoid and to determine whether signs recurred or additional veterinary intervention was needed in the days after initial treatment.

Methods This retrospective study evaluated 73 cats treated for allergic reaction with diphenhydramine alone or in combination with a glucocorticoid at a 24 h emergency and specialty referral veterinary hospital between 1 January 2012 and 31 March 2021.

Results In total, 44 cats were treated with diphenhydramine alone, and 29 were treated with diphenhydramine plus dexamethasone sodium phosphate. The inciting cause was known or highly suspected in 50 patients. Vaccines were the most common (31 patients), followed by insect envenomation (17 cases). No cat in either group progressed to anaphylaxis. There was no difference in resolution of clinical signs between the groups. Follow-up contact was successfully made with 40/73 cat owners. All 40 cats were alive. Eight had persistent signs. There was no difference in the number of cats with persistent signs between groups. Five cats required additional treatment after the initial emergency visit. There was no difference between the two groups for persistent signs at follow-up.

Conclusions and relevance There was no difference in measured outcomes between cats treated with diphenhydramine alone vs those treated with a glucocorticoid in addition to diphenhydramine in this population. The ideal treatment for allergic reactions is unknown. Based on currently available data in human and veterinary literature, glucocorticoids are not indicated to treat acute allergic reactions. The role of antihistamines as part of a symptomatic supportive treatment plan to shorten the duration of signs is unclear at this time and may be considered.

Keywords: Anaphylaxis; antihistamine; corticosteroid; glucocorticoid; steroid; type 1 hypersensitivity reaction

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Introduction

A type 1 hypersensitivity reaction, or immediate hypersensitivity reaction, is mediated by IgE and results in the degranulation of mast cells and basophils.^{1–5} Type 1 hypersensitivity reactions occur after exposure to allergens such as food, drugs, venom, aeroallergens, blood products, vaccines and more.^{1,3–9} The clinical signs seen with type 1 hypersensitivity reactions vary from mild to severe and are dependent not only on the species, but also on the organs affected.^{1,3–12} Some signs seen with mild reactions include pruritus, angioedema and urticaria, whereas severe reactions can result in airway obstruction, hypotension and death.^{1,3–12} Mild reactions are usually

classified as allergic reactions, while severe reactions are called an anaphylactic reaction.^{6,10,12} Given the severity of anaphylaxis, it is important to clinically distinguish it

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from allergic reactions.⁹ Treatment for anaphylaxis primarily consists of epinephrine (adrenaline) and intravenous fluid resuscitation.^{1,2,4,5,9–16}

The treatment of allergic reactions has been investigated in veterinary literature about dogs. In a recent retrospective study, it was noted that there was no difference seen in the response to therapy nor the need for additional intervention when glucocorticoid was added to diphenhydramine for the treatment of allergic reactions in dogs.⁷ Treatment with antihistamines is aimed at downregulating the allergic response and reducing clinical signs such as urticaria, pruritus, erythema and angioedema.^{1,4,12,17–20} The injectable formulations provide a rapid onset of action.^{4,12,20–22} Glucocorticoids downregulate the late-phase eosinophilic inflammatory response and cause transrepression of activated genes that encode proinflammatory proteins.^{4,17,18,22,23} Glucocorticoids are also thought to block the arachidonic acid cascade and may relieve protracted signs and prevent biphasic anaphylaxis.^{1,4,17,22} It is important to note that while many practitioners give glucocorticoids for the immediate reaction, they take 4–6 h for beneficial effects to start, regardless of the route of administration.^{12,18,22,24}

The primary objective of the current study was to report the outcome of the initial treatment of allergic reactions in cats with diphenhydramine alone vs diphenhydramine plus glucocorticoid. We hypothesized that there would be an improvement in clinical signs after the administration of diphenhydramine, but no difference in the resolution of clinical signs or need for additional veterinary intervention after the initial emergency department visit between patients treated with diphenhydramine alone and those treated with diphenhydramine plus a glucocorticoid. The secondary objectives were to report the recurrence of signs and the need for additional veterinary intervention in the days after initial treatment and to determine the incidence of allergic reactions in a 24 h, emergency and specialty referral veterinary practice.

Materials and methods

The medical record database was searched to identify all animals presenting to the emergency department with signs consistent with an allergic reaction between 1 January 2012 and 31 March 2021. The search function of the medical records system was used to search all sections of patient medical records using the following terms: allergic reaction; vaccine reaction; reaction; bee; wasp; insect; sting; envenomation; facial swelling; periocular swelling; periocular edema; urticaria; pruritus; paw swelling; diphenhydramine; dexamethasone sodium phosphate; prednisone; and prednisolone. In addition, a search was conducted of all invoices concluded within the search dates for emergency service visits using the product codes for diphenhydramine, dexamethasone

sodium phosphate, prednisone and prednisolone. The results were subsequently separated by species.

All cats presented to the emergency department between 1 January 2012 and 31 March 2021 with at least one sign consistent with an allergic reaction (defined below) were eligible for inclusion. Cats were excluded if they did not have signs of an allergic reaction, presented with signs consistent with anaphylactic shock, were currently being treated with antihistamines or glucocorticoids for a pre-existing medical condition (reported by the owner as a current medication on intake) or if the medical record failed to document treatments administered at initial presentation. Although patients presenting with anaphylactic shock were excluded from the analysis, a patient presenting with signs of allergic reaction and progression of signs to anaphylaxis after initial treatment with antihistamine (with or without glucocorticoid) was *not* a criterion for exclusion. An allergic reaction was defined as acute onset of muzzle or periocular angioedema, urticaria, generalized erythema with pruritus or paw swelling without trauma. Anaphylactic shock was defined as a patient with an acute allergic reaction requiring epinephrine, oxygen supplementation or intravenous (IV) fluid resuscitation as a part of treatment at initial presentation to treat life-threatening oxygenation, ventilation or perfusion abnormalities.

For cats included in the final analysis, the following data were extracted from the medical records: age; sex; breed; weight; all drugs and doses administered; additional treatments administered; medications prescribed at discharge; presence or absence of signs at follow-up contact post-visit; need for additional veterinary intervention after emergency room visit; suspected inciting event (if known/reported); and the presence or absence of pruritus, facial swelling, urticaria, vomiting, diarrhea, respiratory distress, lethargy and paw swelling as part of the presenting complaint at any time during the visit.

Improvement after the initial treatments and before discharge was recorded as 'yes' if improvement was documented in the medical record, 'no' if the medical record stated there was no improvement and 'unknown' if there was no documentation related to response to initial treatments. Additional treatment before discharge was recorded as 'yes' if additional doses of diphenhydramine or glucocorticoid were administered, if the record clearly documents that either an antihistamine or a glucocorticoid was given due to lack of improvement, or if other treatments were given during the visit. Discharge medications were recorded as 'yes' if medications were dispensed to continue at home or if the discharge instructions directed the owner to continue an over-the-counter medication at home, and 'no' if they were not. When medications were dispensed, or over-the-counter medications were directed to be given, the drug and dose were recorded.

It is standard at the study institution to call the owners of every patient within 2–3 days after discharge. The follow-up conversations are documented in a specific section of the medical record and there are members of staff with time dedicated to this task. When owners cannot be reached, a message requesting a return call with a patient update is left when possible. This section of the medical record was reviewed for all included patients to determine events occurring after discharge. Additional treatment after discharge was defined as worsening, persistent or recurrent clinical signs requiring a return to the emergency department, another veterinary office visit elsewhere, or if additional treatments different from the discharge instructions were administered at home after a phone consultation with the emergency service or primary care veterinarian. If any of these events occurred, it was recorded as 'yes'. It was recorded as 'no' if the owner reported resolution without additional intervention, 'unknown' if the notes were ambiguous about additional treatments after discharge or 'lost' if the follow-up contact could not be made or was not documented. Persistent signs at follow-up were recorded as 'yes' if the owner reported any of the signs were still present, as 'no' if the owner reported the signs were completely resolved and 'unknown' if the owner could not be contacted or if resolution was not documented in the communication notes.

Statistics

Cats receiving antihistamine only (the AO group) were compared to cats receiving both antihistamine and glucocorticoid (AG). Data were analyzed by means of descriptive and inferential methods using commercially available software (Stata Statistical Software version 14; StataCorp). Data were tabulated for descriptive purposes. Data distribution was tested for normality using the Shapiro–Wilk test. The Mann–Whitney U-test was used for continuous variables and Fisher's exact test for categorical data. Values of $P < 0.05$ were considered significant.

Results

During the study period, the emergency and critical care service received 103,237 primary case presentations (this excludes inter-service transfers and recheck/follow-up examinations). From these, the medical records and invoice search identified 2473 animals that had presented for allergic reactions: 147 cats and 2326 dogs. After excluding all dogs, cats with anaphylaxis, incomplete medical records and those receiving diphenhydramine or glucocorticoids for other medical conditions, 73 cats were included in the final analysis.

There were no differences in patient demographics (Table 1) between the AO and AG groups ($P > 0.05$). The inciting cause was known or highly suspected in 50 (68%) cases. Vaccines were the most common suspected cause documented in 31 (42.5%) cases, followed by insect

Table 1 Breakdown of patient demographics

Demographics	AO (n = 44)	AG (n = 29)	Total (n = 73)
Sex			
Female intact	5	1	6 (8.2)
Female spayed	16	10	26 (35.6)
Male intact	1	3	4 (5.5)
Male castrated	23	14	37 (50.7)
Age (years)			
0–1	13	9	22 (30.1)
1–3	11	7	18 (24.6)
3–6	12	6	18 (24.6)
6–9	5	3	8 (11)
>9	3	3	6 (8.2)
Unknown	1	0	1 (1.4)
Weight (kg)			
0–2.5	6	5	11 (15.1)
2.5–4.5	13	10	23 (31.5)
4.5–7	23	13	36 (49.3)
7–10	3	0	3 (4.1)
Breed			
Domestic shorthair	28	21	49 (67.1)
Domestic mediumhair	7	3	10 (13.7)
Domestic longhair	1	1	2 (2.7)
Bengal	2	1	3 (4.1)
Russian Blue	2	0	2 (2.7)
Other (1 of each breed)	5	2	7 (9.6)

Data are presented as n (%)

AO = antihistamine only; AG = antihistamine and glucocorticoid

envenomation in 17 (23.3%) cases and adverse drug reactions in 2 (2.7%) cases. The suspected cause was either not documented or listed as unknown in 23 (31.5%) cases. There was no difference in suspected cause between the AO and AG groups. The most common abnormalities identified on history and physical examination were as follows: facial swelling (n = 33, 45.2%); vomiting (n = 29, 39.7%); lethargy (n = 24, 32.9%); pruritus (n = 19, 26%); generalized erythema (n = 19, 26%); paw swelling (n = 15, 20.5%); and diarrhea (n = 8, 11%). Urticaria was only documented in 1 (1.4%) cat. There were no differences in frequency of these signs between the AO and AG groups.

Although not required for study inclusion, all cats received at least one dose of diphenhydramine. In total, 44 (60%) cats were treated with diphenhydramine alone, and 29 (40%) were treated with diphenhydramine plus a glucocorticoid. Diphenhydramine was administered intramuscularly in all 73 patients at a median dose of 2.0 mg/kg (range 0.2–2.8 mg/kg). The 29 patients that received glucocorticoids as part of the initial treatment were given dexamethasone sodium phosphate via either the

intramuscular (IM) or IV route (median dose 0.23 mg/kg, range 0.06–0.43) and none received glucocorticoids orally. An improvement in clinical signs was noted in 68/73 (93%) cats, 41/44 (93%) in the AO group and 27/29 (93%) cats in the AG group. No cat in either group progressed to anaphylaxis during the visit. There was no difference in the resolution of clinical signs between the groups.

All 73 patients were treated as outpatients. In total, 40 (54.8%) cats received additional treatments during the initial emergency visit. The most common treatments were subcutaneous fluids (19/73, 26%), antiemetic drugs (17/73, 23.3%), pain-relieving medications (12/73, 16.4%) and sedative drugs (7/73, 9.5%; to facilitate examination or remove insect stingers). The remainder of the interventions accounted for 1% (1 cat) each. Aside from the administration of famotidine (3/73, 4.1%) and acepromazine (1/73, 1.4%), none of the additional treatments given are known to affect histamine. There was no difference in the overall number of patients receiving additional treatments between the two groups ($P = 0.63$). Due to small subgroup sizes, comparative statistics were not performed for individual treatments.

A total of 37 (50.7%) patients were discharged with instructions to continue medications at home. Of these 37 cats, 34 were discharged with diphenhydramine only, one with prednisolone only, and two cats with both diphenhydramine and prednisolone. Diphenhydramine was the only antihistamine prescribed, and prednisolone was the only glucocorticoid prescribed. There was no difference in discharge medications between the AO and AG groups ($P = 0.11$).

Follow-up contact was successfully made with 40/73 cat owners: 21/44 (47.7%) in the AO group and 19/29 (65.5%) in the AG group. All 40 cats were alive at the time of contact. Eight (11%) had persistent signs: 3 (6.8%) in the AO group and 5 (17%) in the AG group. There was no difference in the number of cats with persistent signs between the groups ($P = 0.331$). Five cats required additional treatment after the initial emergency visit: two from the AO group and three from the AG group. There was no difference between the AO and AG groups in the number of cats requiring additional treatments ($P = 0.272$).

There were five cats that did not show improvement after initial treatment. All remained cardiovascularly stable and four were discharged home for monitoring with non-specific supportive treatments, such as analgesics, in addition to instructions to continue diphenhydramine three times daily for three more days. The follow-up data are available for three of the four discharged cats, and all were asymptomatic by follow-up. The fifth cat, which did not improve with initial therapy (AO group), was treated 30 mins later with 0.15 mg/kg dexamethasone sodium phosphate IV and failed to improve over the next hour. This cat had generalized erythema, pruritus and mild facial swelling, but remained cardiovascularly stable. He was subsequently treated with 0.01 mg/kg epinephrine

IM, and the record reports that the signs improved significantly over the next 30 mins. No follow-up data are available for this patient.

Discussion

As hypothesized, there was no difference in response to treatment when glucocorticoids were added to diphenhydramine for the treatment of allergic reactions in this population of cats. There was also no difference in the number of patients that had persistent signs at follow-up nor in the number of cats that required additional treatments for persistent signs either before or after discharge from the initial emergency visit. These findings are consistent with findings in humans and a recent study in dogs.^{7,25} All of the animals included in the study received diphenhydramine and, therefore, we cannot draw any conclusions about the association of this drug with resolution of signs.

There is a dearth of information about the occurrence or treatment of allergic reactions and anaphylaxis in feline patients in the primary literature. In humans and dogs, treating the localized signs of an allergic reaction is considered symptomatic relief rather than a life-saving intervention because, while uncomfortable, signs are expected to be self-limiting.^{4,7,9,10,12} As with dogs and people, relieving these signs faster seems a reasonable intervention for the comfort of the patient and the owner. The use of diphenhydramine to treat localized cutaneous signs of allergic reactions is anecdotal, with a reported dose range of 0.5–2 mg/kg parenterally or 2–4 mg/kg orally.²² The median initial dose administered in this study was 2 mg/kg (range 0.2–2.8 IM). Most cats received doses near 2 mg/kg, preventing conclusions about other doses. Historically, H1-antihistamines have been described as H1-receptor antagonists or H1-receptor blockers that downregulate the allergic response, minimizing the clinical impact of histamine release and providing a physiologically justifiable rationale for use in allergic reactions.^{1,4,12,17,22} However, this terminology and physiologic description is outdated and does not accurately reflect the mechanism of action.²⁰ H1-antihistamines are inverse agonists.²⁰ They have a higher affinity for the inactive form of the receptor, binding and stabilizing the receptor in the inactive state and inhibiting interaction with histamine.²⁰ They are relatively ineffective once histamine has bound to the receptor converting it to the active state.²⁰ Thus, antihistamines are much more effective at preventing a histamine reaction (by administration before allergen exposure) than after histamine converts the receptor to the active state, which explains why these drugs are not a very effective treatment for ongoing allergic reactions.²⁰

Diphenhydramine was the only H1-antihistamine prescribed in the current study both for initial treatment and for those receiving additional antihistamines at home after discharge. Diphenhydramine is the only

parenteral H1-antihistamine available at the study institution; therefore, if a clinician chooses to give parenteral antihistamines, diphenhydramine is the only drug available. When antihistamines were prescribed as part of the discharge plan, most clinicians instructed owners to acquire diphenhydramine from a local drug store rather than filling a prescription at the hospital. There were no instances of other antihistamines being recommended in the discharge instructions. As in the recent study in dogs, based on the communication logs, very few owners continued administering diphenhydramine at home. Despite this, most patients went on to have full resolution of signs by the time of follow-up.

Overall, 93% of cats responded to initial treatment regardless of the addition of glucocorticoids to the treatment plan. The mechanism of action for glucocorticoids is such that it takes several hours to be effective; therefore, it makes sense that there was no immediate difference in response between groups.^{4,12,22} There is no published dexamethasone sodium phosphate dose specific for hypersensitivity reactions in cats. The reported dose range for anti-inflammatory purposes in cats is 0.14–0.28 mg/kg/day.²² The median dose administered to the cats in this study was 0.23 mg/kg (range 0.06–0.43). This was the only glucocorticoid administered as part of initial treatment in the AG group. Adverse events associated with glucocorticoid use could not be evaluated due to the inconsistent way the follow-up questions were asked and documented. If prospective studies are performed, this might be a question of interest.

In human literature, administration of glucocorticoids for the treatment of allergic reactions or anaphylaxis is not recommended.^{13–16,25,26} In recent literature, it has been shown that physicians gave glucocorticoids more often than epinephrine, the recommended treatment for anaphylaxis.^{13,15,26} Multiple reviews report that corticosteroids do not reduce the severity of clinical signs or prevent biphasic reactions, which are traditionally the rationale for steroid usage.^{14,26,27} In a retrospective study in people, steroid use in allergy-related emergency visits was not shown to be superior to no steroid use.²⁵ As a result, the use of steroids in veterinary medicine is also likely not indicated.

The current study has several limitations, mostly the result of the retrospective design. All patients received diphenhydramine as part of the initial treatment; therefore, the effect of diphenhydramine (or possibly lack of effect) on the resolution of signs cannot be determined. Because this is a retrospective chart review, the rationale for glucocorticoid administration, when used, could not be determined. Documentation was not standardized to record presenting signs, response to treatment, duration of monitoring after treatment, or follow-up questions and subsequent notation in the medical record. Differences in the severity of signs between treatment groups and how the severity of signs affected individual prescribing and

treatment decisions could not be evaluated. Most experienced emergency practitioners probably have a routine for treating allergic reactions; for some, the routine will include using glucocorticoids, while for others, it will not. There may be a tendency to use glucocorticoids or higher doses of glucocorticoids in patients perceived to have a more severe reaction, making it impossible to determine what role, if any, glucocorticoids played in the patient's outcome (ie, confounding by indication). Perceived severity might also influence what drugs, if any, are prescribed for post-discharge use. Lack of a standardized monitoring period after initial treatment also complicates the interpretation of response to treatment. It is possible that a patient monitored for only a short period might have ultimately responded to treatment without additional intervention if given more time. Alternatively, a patient might show initial improvement and then worsen again if monitored longer. Finally, the follow-up data rely on owners to report the presence or absence of signs, and those signs to subsequently be recorded by the individual on the phone and then interpreted by the investigators extracting data from the records.

Conclusions

The ideal treatment for allergic reactions in cats is unknown. Based on currently available data in human and veterinary literature, glucocorticoids are not indicated to treat acute allergic reactions in cats. The role of antihistamines as part of a symptomatic supportive treatment plan to shorten the duration of signs in cats is unclear at this time and may be considered.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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Resources

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