Fexofenadine Treatment of Atopic Dogs: Preliminary Clinical Results

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Abstract

The purpose of our study was to investigate the efficacy and safety of the antihistamine fexofenadine versus methylprednisolone in dogs with atopic dermatitis. Eight dogs were included in the study and randomly allocated to two groups of four animals. The first group (F) received oral fexofenadine and the second group (M) received methylprednisolone. Over a period of 6 weeks, we evaluated the CADESI (Canine Atopic Dermatitis Extent Severity Index) score and the pruritus score and made measurements of biochemical blood indicators (AP, ALT, AST, urea, creatinine) on three occasions.

The study results did not reveal any statistically significant differences compared to baseline in AST, ALT, AP, urea and creatinine values in any of the treated groups and at any of the time points during the treatment (p > 0.112).

The mean CADESI values and the severity of pruritus were reduced by more than 50% in both groups during the treatment course. There were no statistically significant differences between group M and group F. A statistically significant difference compared to the baseline was found in the reduction of the CADESI score in group F in the sixth week of treatment (p = 0.011). There was also a significant reduction compared to the baseline in the severity of pruritus ingroup M in the third (p = 0.004) and sixth week of treatment (p = 0.022).

Our results indicate the possible use of fexofenadine in the treatment of atopic dermatitis in dogs, as it was demonstrated safe and effective in comparison with methylprednisolone.

Fexofenadine hydrochloride, methylprednisolone, atopic dermatitis, glucocorticoids, antihistamines, antipruritic drugs

Canine atopic dermatitis (atopy) may be best described as a multifactorial disease in which genetically predisposed dogs exhibit a combination of cutaneous IgE-mediated immediate and late phase reactions to environmental antigens (Scott et al. 1995). Atopy is universally recognized and, in areas with fleas, is the second most common hypersensitivity skin disorder of dogs. It probably affects around 10% of the canine population (Flemming 2004). The diagnosis is based on the history, physical examination, ruling out other possible diagnoses, and intradermal testing or serologic allergy testing. For the symptomatic treatment of canine atopic dermatitis, glucocorticoids, antihistamines or their combination are most frequently used. The most frequently used glucocorticoid is prednisolon, but its long-term use can produce serious side effects (Kirk et al. 1995). The responses to antihistamines in dogs with canine atopic dermatitis are very individualized and unpredictable (Scott et al. 1994a, Scott et al. 2001). The efficacy of antihistamines is also unpredictable from results of in vivo and in vitro laboratory studies. For example, although terfenadine markedly inhibited allergen-induced wheal formation in the skin of Ascaris hypersensitive dogs, the same or higher dose of the drug was ineffective for the treatment of pruritus in atopic dogs (Scott et al. 1994b). Similarly, although chlorpheniramine and clemastine failed to inhibit allergen-induced wheal formation in the skin of Ascaris hypersensitive dogs, both drugs are
effective for the control of pruritus in 30% of dogs with canine atopic dermatitis (Scott et al. 1988, Paradis et al. 1991, Scott et al. 1994a). Astemizole, loratadine and terfenadine (when administered at 15 mg/kg every 12 hours) do not appear to be effective in dogs (Kirk et al. 1995). Fexofenadine is a second generation antihistamine. From the data collected in literature it does not have sedative effects in humans, it is very safe to use and it is very effective (Craig 2000). No data are available in literature on the clinical use, efficacy and the optimal therapeutic dose of fexofenadine in animals.

The purpose of our study was to investigate the efficacy and safety of the antihistamine fexofenadine versus methylprednisolone in dogs with atopic dermatitis.

Materials and Methods

Inclusion criteria

The study was performed in accordance with guidelines for the use of experimental animals. Authorisation from the Ethical Committee on animal experimentation of the Veterinary Administration of the Republic of Slovenia (No.: 323-02-525/2005/2) was obtained prior to the start of the study.

The study included 8 dogs older than 6 months of different breeds and sex, with the diagnosis of atopic dermatitis (Table 1). The following inclusion criteria were used:

Prior to the start of the study, basic examinations were carried out to exclude the presence of other possible diseases (parasitic diseases, other allergic diseases). The dogs had to be free of fleas. During the study, they were treated with the long-acting anti-flea product (Frontline Spot-On by Merial, Lyon, France). All dogs were fed an elimination diet during the study period. In each dog, intradermal skin test was performed not earlier than 3 months prior to the start of the study. The clinical diagnosis of atopic dermatitis was based on the evaluation of the major and minor criteria according to Willemse (1986). We considered at least 3 major and 2 minor criteria. The following major criteria were considered:

1. The presence of pruritus
2. Typical location of lesions - lesions on the head (lip inflammation or erythema on the inside of the ear) and/or legs (bilateral cranial pododermatitis) and lichenification of the bending part of the elbow joint and/or extensor part of the carpal joint
3. Chronic or recurrent dermatitis
4. Known breed or family predisposition

Minor criteria:

1. Positive intradermal test finding
2. Onset of first symptoms at the age between 6 months and 3 years
3. Bilateral conjunctivitis
4. Superficial suppurative skin inflammation
5. Face erythema and hyperhidrosis

Non-inclusion and exclusion criteria

1. Dogs with inadequately documented history of the disease and previous therapies and their outcome
2. Dogs with health conditions that would hinder the evaluation of the disease (e.g. cardiologic patients)
3. Dogs with serious liver or kidney dysfunction
4. Planned or accidental pregnancy
5. Dogs with allergic symptoms after flea bite
6. Dogs in which allergy to food was not excluded or had not been controlled with an appropriate diet
7. Dogs with ectoparasites and symptoms of bacterial or fungal skin infection
8. Dogs treated with medicinal products not allowed:
   - Steroids: less than 3 weeks prior to inclusion
   - Antihistamines: less than 14 days prior to inclusion
   - Cyclosporines: less than 30 days prior to inclusion
   - Supplements of essential fatty acids: less than 14 days prior to inclusion
   - Vitamin E supplements: less than 14 days prior to inclusion
   - Antipruritic agents such as serotonin reuptake inhibitors (SRIs) and selective serotonin reuptake inhibitors (SSRIs): less than 14 days prior to inclusion
   - Antiseborrhic, antikeratolytic and antiseptic shampoos: less than 14 days prior to inclusion
   - Immunotherapeutics

Procedure

Eight dogs with confirmed diagnosis of atopic dermatitis were randomly allocated to two groups of 4. The first group received oral fexofenadine at doses of 18 mg/kg body weight once daily (group F). The second group (group M) received oral methylprednisolone at doses of 0.5 mg/kg body weight daily for 5 days, then 0.5 mg/kg body weight every other day. The duration of the treatment was 6 weeks. In this period, the
following evaluation procedures and measurements were performed at 3 time points (at inclusion, after 3 weeks and after 6 weeks): CADESI scoring system, visual analogue scale for evaluation of pruritus and biochemical blood indicators (alkaline phosphatase - AP; alanine transferase - ALT; aspartate transferase - AST; urea; creatinine) (Table 2).

The effects of the treatment were evaluated with the CADESI (Canine Atopic Dermatitis Extent Severity Index) (Olivry et al. 2003) scoring system.

We evaluated the presence and intensity of skin erythema, lichenification and excoriation on 40 skin areas. Each indicator was assessed with a score from 0 to 3 (0 = no lesions). The evaluation was performed at each visit. The sum of the scores obtained for each part of the body was used as the final score and for between-visit comparison.

Dermal pruritus was assessed in each dog based on observations made by the dog owners. Pruritus was evaluated using the visual analogue scale on which the dog owners recorded their evaluation with scoring on a 0 to 100 scale (0 = no pruritus). The dog owners’ evaluation was based on their assessment of the intensity, frequency and duration of pruritus. They were instructed to pay attention to licking of paws and the inguinal region, biting of paws and body, scratching of the head and body, and rubbing of the head and body against objects.

The safety of the medicinal product was assessed by blood tests of liver enzymes, AST, ALT and alkaline phosphatase, and urea and creatinine as indicators of renal function.

Statistical evaluation
Statistical evaluation of the obtained data was performed using one-way Student’s t-test. All values lower than 0.05 were considered statistically significant.

Results
The results of the study are shown in Tables 1 and 2 and in Figs 1 and 2.

Table 1. Dogs, included in the study, randomised to group M (methylprednisolone treated) and to group F (fexofenadine treated)

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient ID</th>
<th>Age (months)</th>
<th>Sex</th>
<th>Breed</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group M</td>
<td>3</td>
<td>9</td>
<td>M</td>
<td>German Shepherd Dog</td>
<td>43.5</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>24</td>
<td>M</td>
<td>German Shepherd Dog</td>
<td>22.1</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>16</td>
<td>M</td>
<td>Boxer</td>
<td>29.7</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>60</td>
<td>F</td>
<td>Russian Terrier</td>
<td>37.0</td>
</tr>
<tr>
<td>Group F</td>
<td>5</td>
<td>47</td>
<td>F</td>
<td>Chow Chow</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>24</td>
<td>M</td>
<td>mongrel</td>
<td>37.0</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>45</td>
<td>M</td>
<td>Shar Pei</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>15</td>
<td>M</td>
<td>Great Dane</td>
<td>69.0</td>
</tr>
</tbody>
</table>

Table 2. Mean values of blood indicators, CADESI and pruritus at visits 1, 2 and 3 (start of treatment, after 3 weeks of treatment and after 6 weeks of treatment) for both groups

<table>
<thead>
<tr>
<th></th>
<th>AST</th>
<th>ALT</th>
<th>AP</th>
<th>Urea</th>
<th>creatinine</th>
<th>CADESI</th>
<th>pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Visit 1</td>
<td>0.79</td>
<td>1.06</td>
<td>1.28</td>
<td>0.92</td>
<td>0.79</td>
<td>1.13</td>
<td>3.68</td>
</tr>
<tr>
<td>Visit 2</td>
<td>0.47</td>
<td>0.84</td>
<td>2.04</td>
<td>0.65</td>
<td>1.00</td>
<td>0.98</td>
<td>4.23</td>
</tr>
<tr>
<td>Visit 3</td>
<td>0.58</td>
<td>0.87</td>
<td>1.15</td>
<td>0.82</td>
<td>0.91</td>
<td>0.84</td>
<td>5.63</td>
</tr>
</tbody>
</table>

Legend: AP; alkaline phosphatase, ALT; alanine transferase, AST; aspartate transferase; M; group M, F; group F

AST
The mean AST value was within the physiological range between visits 1 and 2 and 1 and 3 in both groups of dogs. In neither group, changes from the baseline were of statistical significance neither at visit 2 nor at visit 3 (group M; p = 0.223 and p = 0.498, respectively; group F; p = 0.640 and p = 0.707, respectively). The between-group comparison after each visit revealed no differences between the groups at visit 1 (p = 0.306) and at visit 2 (p = 0.145). However, a significant difference between the groups was found at visit 3 (p = 0.049).
In group M, there was an increase in the mean ALT value from the baseline at visit 2, followed by a small reduction at visit 3. In group F, first a reduction in the mean ALT value was observed and an increase at visit 3; however, it did not reach the baseline value. All values were within the physiological range. Deviations from the baseline within the groups were of no significance neither at visit 2 nor at visit 3 (group M: $p = 0.648$ and $p = 0.985$, respectively) (group F: $p = 0.724$ and $p = 0.958$, respectively). The between-group comparison after each visit also demonstrated no differences between the groups (visit 1: $p = 0.354$; visit 2: $p = 0.186$; visit 3: $p = 0.352$).

ALT

In group M, there was an increase in the mean ALT value from the baseline at visit 2, followed by a small reduction at visit 3. In group F, first a reduction in the mean ALT value was observed and an increase at visit 3; however, it did not reach the baseline value. All values were within the physiological range. Deviations from the baseline within the groups were of no significance neither at visit 2 nor at visit 3 (group M: $p = 0.648$ and $p = 0.985$, respectively) (group F: $p = 0.724$ and $p = 0.958$, respectively). The between-group comparison after each visit also demonstrated no differences between the groups (visit 1: $p = 0.354$; visit 2: $p = 0.186$; visit 3: $p = 0.352$).

AP

In group M, there was an increase in the mean value of alkaline phosphatase at visit 2 and a small decrease at visit 3, differently than in group F where a constant decrease was observed compared to the baseline value. The values were within the physiological range in both groups. The within-group differences from baseline were of no significance neither at visit 2 nor visit 3 (group M: $p = 0.810$ and $p = 0.938$, respectively; group F: $p = 0.950$ and $p = 0.813$, respectively). The between-group comparison after each visit also revealed no differences between the groups at visit 1 ($p = 0.454$) and 2 ($p = 0.967$) and 3 ($p = 0.841$).
**Urea**

The mean urea value in group M was constantly increasing up to visit 3, whereas in group F it remained unchanged. However, all values remained within the physiological range. The within-group difference from the baseline was of no significance (group M: $p = 0.804$ and $p = 0.112$ at visits 2 and 3, respectively; group F: $p = 0.993$ and $p = 0.999$ at visits 2 and 3, respectively). The between-group comparison after each visit revealed a significant difference between the groups at visit 1 ($p = 0.038$). However, no significance was observed at visits 2 ($p = 0.116$) and 3 ($p = 0.560$).

**Creatinine**

The mean creatinine value was decreasing throughout the study in group M, while in group F an increase was observed at visit 2, which was maintained to the end of the study. All differences were within the physiological range. The differences within the groups M and F were of no significance neither at visit 2 nor at visit 3 (group M: $p = 0.909$ and $p = 0.873$ at visit 2 and 3, respectively; group F: $p = 0.822$ and $p = 0.843$ at visits 2 and 3, respectively). The between-group comparison after each visit did not reveal a significant difference at visit 1 ($p = 0.362$), while significant differences were found at visit 2 ($p = 0.042$) and visit 3 ($p = 0.039$).

**CADESI score**

The mean CADESI scores decreased in both groups throughout the study period (Fig. 1). No statistically significant differences from baseline were found at visit 2 in any of the groups ($p = 0.470$ in group M and $p = 0.102$ in group F). However, a comparison of the obtained values, performed at the end of the study period revealed a significant difference from the baseline in group F ($p = 0.011$). In group M, no significant difference from the baseline was found at the end of the study period ($p = 0.171$). The between-group comparison after each visit did not show a significant difference neither at visit 1 ($p = 0.898$) nor at visits 2 ($p = 0.500$) and 3 ($p = 0.111$).

**Pruritus score**

The severity of pruritus was markedly reduced compared to the baseline in group M at visit 2. This was followed by a slight increase observed at visit 3 (Fig. 2). The results demonstrated a significant decrease compared to the baseline in the severity of pruritus in group M at visits 2 ($p = 0.004$) and 3 ($p = 0.022$). In group F, the severity of pruritus was decreasing throughout the study period but compared to the baseline this decrease was of no significance ($p = 0.668$ and $p = 0.374$ at visits 2 and 3). The between-group comparison after each visit did not demonstrate a significant difference neither at visit 1 ($p = 0.625$) nor at visits 2 ($p = 0.078$) and 3 ($p = 0.736$).

**Discussion**

The study was carried out using tablets of 180 mg fexofenadine. The decision on the selected dosage (18 mg/kg body weight) was based on the still acceptable number of tablets to be taken at a single dose and under consideration of dose ranges of other antihistamines used in humans as well as animals.

The results obtained so far demonstrate that there are no significant within-group differences with regard to AST and ALT at different time intervals during the treatment. The significant difference ($p = 0.049$) between groups M and F in the AST value at visit 3 was assessed as clinically non-significant, as AST values in group F were higher at the baseline. All AST and ALT values were within the physiological range in dogs. A statistically significant difference between the groups was observed in the baseline
mean urea value, which was markedly lower in group M. Certainly, at randomisation we could not consider every single parameter separately and, in a small number of dogs, there was a greater influence of single values. However, our values were within the physiological range.

It is of special importance that at visits 2 and 3 we did not find any statistically significant differences between group M and group F, which could be attributed to the effect of one or the other active substance; therefore, it is our opinion that none of the active substances had a negative influence on the urea value in treated dogs. In alkaline phosphatase, the between-group differences and differences between individual visits were not of statistical significance and were within the physiological range for dogs, meaning that none of the active substances had an influence on the deviation in alkaline phosphatase values in treated dogs.

In group F, the dog No. 9 had a creatinine value (184 µmol/l) above the physiological level already at visit 1. High serum creatinine values may appear in particular in reduced glomerular filtration, while they are less affected by dietary factors and muscle diseases (Willard et al. 1999). Since this was not an exclusion criterion and the animal did not show clinical signs of renal failure, it was not excluded from the study. However, due to the small number of included animals it had a great influence on the mean creatinine value in group F. This led to significant differences between group M and group F. As the mean values were within the physiological range, we concluded that the difference between the groups was of no clinical importance.

The comparison of the CADESI score between group M and group F in the sixth week of treatment revealed a significant difference from the baseline in group F ($p = 0.011$). In group M, no significant difference from the baseline was found at the end of the study ($p = 0.171$). This finding is an indication of good efficacy of fexofenadine compared to methylprednisolone. Authors of a similar study (Olivry et al. 2003) defined significant difference in the CADESI score as 50% reduction (CADESI$_{50}$) compared to the baseline. Taking into account the recommendations of these authors, we may assess both active substances as sufficiently effective in the treatment of dogs with atopic dermatitis. In group F, the study results even revealed a statistically significant decrease of the CADESI score between visits 1 and 3.

In group M, we observed a statistically significant reduction from the baseline in the severity of pruritus at visits 2 and 3. In group F, there was a continuous reduction in the severity of pruritus, but of no statistical significance. Evaluating the obtained results in a similar way as did the above group of investigators (Olivry et al. 2003), we find out that the severity of pruritus was reduced by more than a half (pruritus$_{50}$) over the period of 6 weeks in both groups, therefore we can conclude that both active substances tested are sufficiently effective to be used in the treatment of dogs with atopic dermatitis. Considering that the assessment of pruritus was obtained from the owners of the animals and was therefore a subjective assessment, a somewhat more critical evaluation of thus obtained results is required.

In view of the results of our study, we can conclude that none of the investigated active substances resulted in any deviations from the physiological values of biochemical indicators (AST, ALT, AP, urea, creatinine) in blood samples of the treated dogs. We assessed both active substances as safe for a short-term use. They were effective in reducing both the severity of pruritus and the presence of skin lesions in dogs with atopic dermatitis.

The preliminary results of the study indicate the possibility of including fexofenadine in the doctrine of treating atopic dermatitis in dogs. Further studies will be required in order to increase the reliability of our conclusions and to confirm the results obtained in our study.
Předběžné výsledky léčby atopických psů fexofenadinem

Cílem naší studie bylo zjistit účinnost a bezpečnost antihistaminika fexofenadinu ve srovnání s methylprednisolonem u psů s atopickou dermatitidou. Do studie bylo zahrnuto osm psů, kteří byli náhodně rozděleni do dvou skupin po čtyřech zvířatech. První skupina (F) dostávala orálně fexofenadin a druhá skupina (M), dostávala methylprednisolon. Po dobu 6 týdnů jsme třikrát hodnotili index CADESI (index rozsahu a závažnosti atopické dermatitis u psů) a index pruritu a měřili biochemické krevní ukazatele (AP, ALT, AST, moč, kreatinin). Výsledky neprokázaly statisticky významné rozdíly v porovnání s počátečním vyšetřením v hodnotách AST, ALT, AP, moči a kreatinínu v žádném z ošetřovaných skupin a v žádném bodě v průběhu léčby ($p > 0,112$).

Průměrné hodnoty indexů CADESI a pruritu se u obou skupin v průběhu terapie snížily o více než 50%. Mezi skupinou M a skupinou F nebyly žádné statisticky významné rozdíly. Významný rozdíl se v srovnání s počátečním vyšetřením se nacházel ve snížení indexu CADESI u skupiny F v šestém týdnu léčby ($p = 0,011$). Ve srovnání s počátečními hodnotami došlo také k významnému snížení pruritu u skupiny M v třetím ($p = 0,004$) a šestém týdnu léčby ($p = 0,022$). Předběžné výsledky studie naznačují možné využití fexofenadinu při léčbě atopické dermatity u psů, neboť ve srovnání s methylprednisolonem se prokázal jako bezpečný a účinný.

References
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