Phytotherapy of chronic dermatitis and pruritus of dogs with a topical preparation containing tea tree oil (Bogaskin®)

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Summary

Localised dermatitis, for example unspecific eczema or skinfold pyoderma, is a very common diagnosis in dogs. Typical and impressive complaints are pruritus, erythema, erosion and oozing surface. With respect to the underlying disease dermatological treatment is indicated, usually based on antimicrobial and antipruriginous active substances, it can include transient glucocorticoids. An effective and safe alternative might be a phytotherapeutic topical preparation containing tea tree oil. Tea tree oil exerts both antimicrobial and antipruriginous effects. In an open multicenter study efficacy and safety of a standardized 10% tea tree oil cream applied thinly and twice daily for 4 weeks was tested in 53 dogs with chronic dermatitis, particularly non-specific eczema, allergic dermatitis, interdigital pyoderma, acral lick dermatitis and skinfold pyoderma. Analysis of efficacy assessed by investigating veterinarians showed a good or very good response to treatment for 82% of the dogs, significant at a 5% level (p = 0.05). At the end of the study a strong and significant reduction (p = 0.001) as well as disappearance of major symptoms were observed. Only two adverse events (local reactions) possibly related to tea tree oil occurred during therapy. Consequently the tested study medication (Bogaskin®) can be considered an alternative for uncomplicated and localised dermatitis in dogs. Bogaskin® might allow reduction of other pharmaceutical products, perhaps even replace standard therapy.

Zusammenfassung

Introduction

Pruritus, erythema, papules, pustules, vesicles, urticaria, oozing surface, erosion and alopecia constitute typical clinical symptoms of dogs suffering from various forms of chronic dermatitis, which cause the owners to consult a veterinarian. Dermatitis is a very common diagnosis. The prevalence of primary dermatological disorders has been shown to be more than 10% of all consultations in veterinary practices (Lund et al., 1999). Including primary as well as secondary (accompanying) forms frequency might exceed 50% of all consultations (Nagata, 2000). Concerning the primary diagnoses, most important are the clinical manifestations with or without pruritus of non-specific eczema, interdigital or skinfold pyoderma, allergic dermatitis and acral lick dermatitis (Lund et al., 1999). From a pathophysiological viewpoint, dermatitis represents an acute or chronic inflammation of the skin, involving both molecular and cellular defense mechanisms thereof. It is caused by a variety of external factors such as allergens, infestations (parasites) and superinfections (bacteria, fungi, viruses e.g. *Staphylococcus intermedius* or *Malassezia pachydermatis*) or traumata (Nagata, 2000; Bigler, 1994; Mason, 1997; Mason and Evans, 1991). Dermatitis may occur concomitantly with internal diseases and additionally, dietary factors may have a role in maintenance of healthy coat and skin and may contribute to the etiology (Lloyd and Marsh, 1999; Bigler, 1994).

Therapy starts following an accurate clinical diagnosis, considering breed, environmental factors, nutritional and eventually laboratory measurements (Bigler, 1994; Nagata, 2000). Pharmacological and dermatological standard therapies are antiparasitica, antibiotic, antimycotica and glucocorticoids, administered both topically and systemically (Mueller, 1999). Topical and systemic glucocorticoids are the strongest anti-inflammatory substances, responsible for subsequent clinical adverse reactions, e.g. the inhibition of wound-repair-processes, diabetes, cushing syndrome or development of resistance (Bigler, 1994; Scott et al., 1995). Because of known side-effects and expected adverse events of cortisone-like substances and antibiotics, pet owners and veterinary surgeons are looking for safe and effective alternatives, which might allow an interruption or even a withdrawal of therapy with chemical pharmaceutical products. In recent years and parallel with developments in human medicine, interest in herbal medicinal products is increasing, with definite expectations regarding effective veterinary phytotherapy (Heinze, 1998; Reichling and Saller, 2001; Smith-Schaltwijk, 1999).

Tea tree oil, the volatile oil of the Australian tree *Melaleuca alternifolia*, exerts strong antimicrobial as well as antipruriginous activities (Galle-Hoffmann and Koenig, 1999; Saller and Reichling, 1995; Saller et al., 1998). Basis for these actions are lipophilic substances (monoterpenes), which interact with biological membranes or penetrate tissue and cell membranes (Cox et al., 2000; Saller et al., 1998). Several clinical studies in humans and numerous experimental studies have shown the efficacy and safety of tea tree oil in the treatment for dermatological indications (Saller et al., 1998; Ernst et al., 2000).

Based on these data, a topical phytotherapeutic preparation (Bogaskin®, Bogar AG, Zürrich) has been registered for the treatment of chronic dermatitis of dogs. It contains 10% of a defined standard quality of tea tree oil as active constituent in an oil-in-water, user-friendly creamy emulsion. An open, multicenter study was conducted to investigate safety and efficacy of this herbal medicinal product for topical treatment of chronic or allergic dermatitis with or without pruritus in dogs.

**Animals, Materials and Methods**

Fifty-three (53) cases of male and female dogs suffering from chronic and/or allergic dermatitis...
with or without pruritus were enrolled in the study by 12 veterinary surgeons in 10 veterinary practices. For the diagnosis the veterinarian had to define the chronic clinical manifestation at the entry visit, where multiple answers were possible (e.g. one case could exhibit several conditions). Exclusion criteria were corticosteroids, antibiotics or phytomedicines administered during 2 weeks before starting as well as during the study. Generalized dermatitis, that needed parenteral therapy was excluded. Following written informed consent of their owners, dogs were enrolled in the study.

**Study drug and administration**

The study drug is a 10% oil in water creamy emulsion of tea tree oil from the Australian tea tree *Melaleuca alternifolia*, provided by Bogar AG, Zürich, in coated aluminium tubes containing 30 g (Bogaskin®). Water content of the creamy emulsion is high (65%) to ensure rapid penetration into the skin. The cream is produced according to good manufacturing practise (GMP). Tea tree oil is obtained from the leaves and terminal branchlets by steam distillation. Its quality meets the requirements of ISO 4730 as well as of the DAC 99 CT-019 (Deutscher Arzneimittel Codex 1999), setting a minimum content of 30% terpinene-4-ol and a maximum content of 15% for 1.8 cineole. Other constituents of this tea tree oil are: 1–6% alphapinen, <3.5% sabinen, 5–13% alpha-terpinen, 0.5–4% limonen, 10–28% gamma-terpinen, 0.5–12% p-cymene, 1.5–5% terpinolen, <7% aromadendrene, 1.5–8% alpha-terpineol. Because of the effective antimicrobial activity of tea tree oil, the finished product contains no preservatives. The owners of the animals had to apply the study drug thinly, twice daily on the effected area for 4 weeks. A dose approximately equivalent to 25 mg of cream (2.5 mg tea tree oil) per cm² of skin was applied. The treatment had to be continued for 4 weeks, even after symptoms had disappeared.

**Evaluation of efficacy and safety**

The primary efficacy parameter was the evaluation of the severity of chronic dermatitis by the investigating veterinary surgeon, through comparing the chronic clinical status in each animal before and after 4 weeks of treatment. Secondary efficacy parameters were determined before treatment (first visit) and at the final visit after 28 days by evaluating incidence and severity of symptoms: pruritus, erythema, papules, pustules, vesicles, urticaria, oozing surface, pus, scabs, erosion, alopecia, skin thickening, scaliness and hyperpigmentation. Each symptom was evaluated by the investigator according to the scores “none”, “slight”, “moderate” or “severe”. A facultative interim visit for the evaluation of symptoms was conducted after 2 weeks (15±3 days) of treatment. In addition, the pet owner kept a patient diary in which the twice-daily application of study drug was documented. For the evaluation of safety all adverse events that occurred during the study had to be documented.

**Biometrical aspects**

Data from all animals, which received the study drug, are included in the efficacy as well as the safety evaluation. Each animal was its own control in the chronic steady-state. Continuous variables were described with mean, standard deviation, median, inter-quartile ranges, minimum and maximum values; discrete variables were described with frequency in each category and percentage of the values in regard to all non-missing values of that variable.

The primary efficacy variable (5%, 2-sided level of significance) was the overall evaluation of severity of chronic dermatitis by the investigator. The 95% confidence interval of the number of animals reporting either a “good or a very good” as opposed to “moderate or severe” judgement was calculated. Secondary efficacy variables were assessed by comparing symptoms at the end and at the beginning of the study. Reduction of incidence and/or of severity of symptoms between visits was statistically evaluated using Bowker’s test. This test is an extension of McNemar/chi-square test and compares the frequency distribution of the severity of a symptom before and after treatment in the chronic steady state situation (Bowker 1948, Zar 1999). For the safety evaluation between visits the 95% confidence interval for the overall tolerability evaluation by the veterinarian of “good or a very good” as opposed to “moderate or severe” was calculated. Statistical calculations were performed with SAS 6.12.

**Results**

**Demographic data**

Animals were selected by 12 investigators in 10 centres, which were practicing veterinarians in Switzerland. Fifty-three dogs were enrolled in the study. The mean age was 5.7 years and mean weight 24 kg; 45% of them were male and 55% female animals (Tab. 1). The duration of complaints was more than 1 year for 42%, 2 months up to 1 year
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16% and up to 2 months 42% of the dogs. The veterinary surgeons indicated one or more clinical diagnoses for each dog (multiple answers). In all there were 80 diagnoses of chronic and/or allergic dermatitis for the enrolled 53 cases at study entry (Fig. 1). Most numerous were non-specific eczema indicated in 30 cases (38%), lick dermatitis 21 (26%) and allergic dermatitis 20 (25%), then followed inter-digital pyoderma 5 (6%) and skin fold pyoderma 4 (5%).

Efficacy

The primary parameter of overall efficacy (per protocol population: 51 dogs; in two cases CRF was not completed for evaluation of global efficacy) was assessed by the investigators in 82% of all dogs as “very good” or “good”, as “moderate” in 7.8% and as “unsatisfactory” in 9.8% after 4 weeks of treatment. This evaluation supports the positive efficacy significantly at the 5% level (P = 0.05) with a 95% confidence interval between 72% and 92%.

Moreover, the treatment with the tea tree oil preparation significantly (P ≤ 0.001 for 6 symptoms and P ≤ 0.01 for 3 symptoms) reduced the incidence and/or severity of the symptoms pruritus, erythema, pustules, oozing surface, pus, scabs, erosion, alopecia and skin thickening in the chronic clinical state (Tab. 2). During the study, a continuous improvement of complaints was observed. Figure 2 shows the progress of declining severity of 4 major symptoms during the course of the 4 weeks treatment. As was to be expected, parallel to the reduction of severity of symptoms there was a reduction in the percentage of dogs, showing symptoms during course of study at day 15 and at day 28 at the end of study. At study completion, pruritus had totally disappeared in 72%, erythema in 79% and erosion and oozing surface in 94% of the dogs (Fig. 3). More distinct results were observed after 15 and 28 days of treatment in cases of dogs with initially moderate and severe symptoms (Fig. 4). Therefore the majority of the dogs were free from their most disturbing symptoms at the end of the study, indicating that the chronic dermatitis was practically healed in nearly 70% of the cases. Three dogs were excluded from efficacy, but not from safety evaluation after concomitant treatment. This not-allowed treatment was considered a deviation and included products containing essential fatty acids, fipronil (topical ectoparasiticide) and a topical cleansing lotion. In these patients, the effects of tea tree oil might have been confounded.

Safety

Safety was primarily evaluated by the investigator, based on the occurrence of adverse events and their nature. The overall tolerability was evaluated for 52 dogs (one original CRF was not completed for overall safety evaluation). The overall tolerability was assessed in 85% of dogs to be “good” or “very good”, for 13% as “moderate” and for 2% as “unsatisfactory”. Adverse effects were reported for 9 dogs: hyperaemia/irritation and pruritus (n = 2), deterioration of symptoms or pain (n = 2), hyper-pigmentation, discoloration of hair or dull new hair (n = 5). Forty-seven dogs completed the study. Three dogs had discontinued for adverse reactions (hyperaemia/irritation, deterioration of symptoms, pain).
and 4 dogs had discontinued the treatment for poor efficacy, poor owner compliance, persistent licking of the study medication or inter-current disease. Only 2 of the 9 dogs with adverse effects were assessed as possibly causally related to the application of the study preparation. One dog showed local irritation and hyperaemia after application of the study drug and was discontinued from the study. Another dog showed slight reversible hyperaemia, erythema and pruritus at the site of drug application at the beginning of study, however continued the study.

Figure 2: Incidence of symptoms (chart A: pruritus, chart B: erythema, chart C: erosion, chart D: oozing surface) and grade of severity at the beginning, after 15 and after 28 days of the 4-week study with 10 % tea tree oil cream (Bogaskin) in 53 cases of dogs with chronic dermatitis (in % of study population). The reduction of severity was significant for each symptom on day 28 as compared to the beginning of study.

Figure 3: Incidence of symptoms characteristic for chronic dermatitis before and after 28 days of treatment with 10 % tea tree oil cream (Bogaskin) in 53 cases of dogs with chronic dermatitis (in % of study population).
Discussion

The results of this study showed a strong and significant reduction and also disappearance of some of the most troublesome symptoms: pruritus, erythema, erosion, and oozing surfaces in canine chronic dermatitis or eczema after 4 weeks of topical treatment with the tested 10% tea tree oil cream Bogaskin®. Each animal was its own control in the chronic steady-state, therefore a placebo-control group was not integrated in this study. In a case of clear diagnosis the standard therapy e.g. antibiotics should by no means be substituted. Mueller (1999) reviewed advantages and disadvantages of conventional standard therapies for dermatitis with pruritus in dogs. However, in many cases of an unclear or only suspected diagnosis and in moderately active disease, tea tree oil might be an antibacterial, antifungal, and an effective antipruriginous alternative. Additionally, the regular incidence and severity of adverse effects of chemically defined substances might be diminished and so the treatment might attract interests of veterinary surgeons and subsequently of dog owners.

The medicinal properties of the leaves of the Australian Myrtaceae Melaleuca alternifolia are already well known since several thousand years. More recently its distilled product, the tea tree oil, has been introduced. Based on a well documented spectrum of antimicrobial actions (Saller et al., 1995, 1998), modern controlled studies in humans have meanwhile shown efficacy in various dermatological indications, as acne, tinea pedis, onychomycosis (Basset et al., 1990; Tong et al., 1992; Buck et al., 1994; Syed et al., 1999). In these studies, the superiority or equivalence of tea tree oil evaluated by clinical symptoms in comparison to placebo or positive controls has been shown. Concentrations of tea tree oil products ranged from 5 up to 100% (undiluted) and the duration of treatment ranged from 4 weeks to 3 months. However, based on the lay press’s numerous reports of tea tree oil as a “cure of all”, further intensive investigation of efficacy and safety of tea tree oil should be demanded (Ernst and Huntley, 2000; Galle-Hoffmann and Koenig, 1999; Saller et al.,

Figure 4: Reduction of symptoms (%) in cases of dogs with initial moderate and severe symptoms after 15 days (chart A) and after 4 weeks (chart B) of treatment with 10% tea tree oil cream (Bogaskin®).
1995, 1998). Important components of tea tree oil are monoterpenes, mainly about 40% of terpinene-4-ol, further α- and γ-terpinene and 1,8-cineole. The qualities of tea tree oil are defined according to the content of terpinene-4-ol and 1,8-cineole, whereby the quality may improve with increasing content of terpinene-4-ol and decreasing content of 1,8-cineole (Altmann, 1989; Galle-Hoffmann and Koenig, 1999; Saller et al., 1998). Physical properties of the strongly lipophilic, highly surface-active monoterpenes allow distribution in biological membranes with various stabilizing or destabilizing membrane effects. On one hand this causes sensations of cold on skin and mucous membranes, and by this way exerting an antipruriginous action. On the other hand terpenes are penetrating into tissue and cell membranes, influencing the metabolism of microorganisms and so exerting antimicrobial effects (Altmann, 1989; Cox et al., 2000; Saller et al., 1995). In vitro studies have shown further antibacterial antifungal and antiviral actions against numerous organisms, well known for their pathogenicity, e. g. the bacteria Escherichia coli, Enterobacter spec., Enterococcus spp., Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus spec. the fungi Aspergillus niger, Candida albicans (Reichling et al., 1997), canine Malassezia pachydermatitis (Weseler et al., 2002), Trichomonas vaginalis, Trichophyton mentagrophytes, T. rubrum and Trichosporon cutaneum (Saller and Reichling, 1995; Saller et al., 1995), and the herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2) (Schnitzler et al., 2001).

In man monoterpenes are rapidly absorbed after topical application and excreted to 60–80% as glucuronides. Some reports on toxic effects are due to undiluted tea tree oil possibly contaminated with degradation products and/or to excessive use at high concentrations or with a high frequency of application. However, all toxic effects are generally reversible without sequelae (Reichling et al., 1997; Villar, 1994). There are several reports of “tea tree oil poisoning” in cats, which were characterized by symptoms of stumbling, emaciation, trembling, nervousness and weakness. The toxicity may arise from the fact that felines are incapable of glucuronidization (glucuronide metabolism) and the tea tree oil components can be excreted only very slowly from their bodies (Villar et al., 1994; Reichling and Saller, 2001). It cannot be excluded that degradation products in “old” tea tree oil, which may accumulate in the body, also play a role in the poisoning of cats. Several contributions reported allergic reactions due to the use of products. Today the allergic potential of tea tree oil attributed to degradation (photo- or autoxidation) products of monoterpenes, which might occur following inappropriate storage conditions, that allow formation of peroxides, epoxides and endoperoxides (Galle-Hoffmann and Koenig, 1999; Harkenthal et al., 1998, 2000; Hansen et al., 1999; Saller et al. 1998; Southwell et al., 1997). Under this respect, application of the emulsion in a coated aluminium tube with safety lock, as for Bogaskin®, is a technical “necessity”.

Given the positive results of our investigation, the study medication containing 10% tea tree oil cream for topical use (Bogaskin®) has to be considered as an appropriate alternative in uncomplicated chronic dermatitis in dogs. Its use might reduce dose, allow an interruption or even withdrawal of therapy of chemically defined products. However, the therapeutic success has to be confirmed by the animal owners or veterinary surgeons. For the therapy of dogs with localised dermatitis, as unspecific eczema or skinfold pyoderma, it is recommended to apply Bogaskin®, containing 10% tea tree oil, thinly and twice daily on the affected area. This application corresponds to approximately 25 mg Bogaskin®/cm² skin. After reduction or healing of symptoms has been observed, generally after 2 to 4 weeks, treatment should be continued for about 2 days.

Acknowledgement

We wish to thank all investigating veterinarians for the accurate performance of this study: Dr. med. vet. K. Brunner, Dr. med. vet. P. Fehlmann, Dr. med. vet. J. Fitzi, Dr. med. vet. C. Hohler, Dr. med. vet. O. Scherrer, Dr. med. vet. A. Huber, Dr. med. vet. A. Jost, Dr. med. vet. H. Radke, Dr. med. vet. H. Schmückel, Dr. med. vet. W. Schönemberger, Dr. med. vet. W. Schönholzer, Dr. med. vet. R. Tschäppät.

Fitzi, Fürst-Jacker, Wegener, Saller, Reichling, Band 144, Heft 5, Mai 2002, 223–231
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Phytolosphére de la dermatite chronique et du prurit au moyen d’huile de théier

Le diagnostic de dermatite localisée est très souvent établi chez le chien. Les symptômes typiques sont prurit, un érythème, des érosions et des blessures ultérieures. Suivant la cause de la maladie, un traitement dermatologique est appliqué, normalement à l’aide de médicaments antimicrobiens et contre le prurit. Dans la plupart des cas, des glucocorticoïdes sont aussi temporairement utilisés. Un médicament phytothérapeutique qui contient de l’huile de théier comme principe actif pourrait s’avérer être une alternative thérapeutique efficace. L’huile de théier agit aussi bien comme antimicrobien que pour soulager le prurit. Dans une étude ouverte incluant plusieurs cliniques, l’efficacité et la sécurité d’une crème standard contenant 10% d’huile de théier a été testée chez 53 chiens atteints d’une dermatite chronique, en particulier un eczéma non spécifique, une dermatite d’origine allergique, une pyodermie interdigitale, une pyodermie des plis de la peau et une dermatite par le moyen d’un albero da tè. La crème a été appliquée deux fois par jour pendant quatre semaines sur les régions atteintes. L’analyse de l’efficacité a révélé que 82% des chiens ont très bien réagi au traitement (p = 0.05). L’examen final au terme de l’étude a démontré une diminution significative (p = 0.001) et marquée et une régression presque totale des symptômes typiques. Des effets secondaires (réactions locales), peut-être dûs à l’huile de théier, ont été observés seulement chez deux chiens. Le médicament à base de plantes (Bogaskin®) examiné peut être considéré comme alternative valable pour les dermatites sans complications et non généralisées chez le chien. Avec l’utilisation du Bogaskin®, l’emploi d’autres médicaments peut être réduit et éventuellement éliminé.

References


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