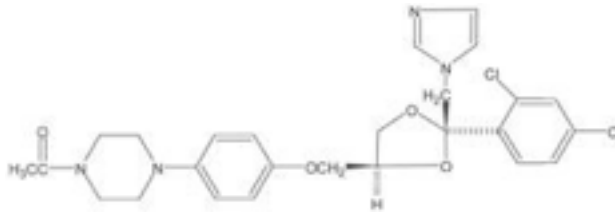


CLINICAL AND SCIENTIFIC DOCUMENTATION SUBSTANTIATING THE SAFETY AND EFFICACY OF ANTISEPTIC & ANTIFUNGAL SHAMPOO

Ketoconazole

Ketoconazole is an imidazole antimycotic. Its fungistatic effect is based primarily on enzyme inhibition due to a bond with the cytochrome P450. It thus inhibits, amongst others, biosynthesis of ergosterol and thereby alters the permeability of the fungal cell membranes.

Ketoconazole is cis - 1 - acetyl - 4 - [4 - [[2 - (2,4 - dichlorophenyl) - 2 - (1H - imidazol - 1 - ylmethyl) - 1,3 - dioxolan - 4 - yl]methoxy]phenyl]piperazine and has the following structural formula:



The azoles are classified as imidazoles (miconazole, econazole, clotrimazole and ketoconazole) or triazoles (fluconazole, itraconazole and voriconazole) according to whether they contain, respectively, two or three nitrogen atoms in the five-member azole ring. The azole class has become the initial treatment of choice for all but the most rapidly progressing and most severe systemic fungal infections.

Fungicidal Activity

Ketoconazole is indicated for topical use or orally, with broad therapeutic potential for the treatment of superficial fungal infections and systemic. The distribution of ketoconazole is limited and their penetration of the liquid cerebrospinal is minimal.

Imidazoles act by interfering with cell wall formation in fungal and yeast organisms, which increases cellular permeability, thus suppressing metabolic function and inhibiting growth. There has also been evidence that ketoconazole exerts an inhibitory effect on keratinocytes in culture.

The antimycotic activity of ketoconazole against fungi *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum* and *Blastomyces dermatitidis* is reached at concentrations of 0.125 mg / m up to 5. mg / m. The corresponding values for *Sporothrix schenckii*, *Candida* sp and *Aspergillus* sp range from 6mg / m to concentrations equal to or greater than 100 mg / m. (Sand & Mandell, 1987; LACAZ & BLACK, 1991, Richardson & Warnock, 1993).

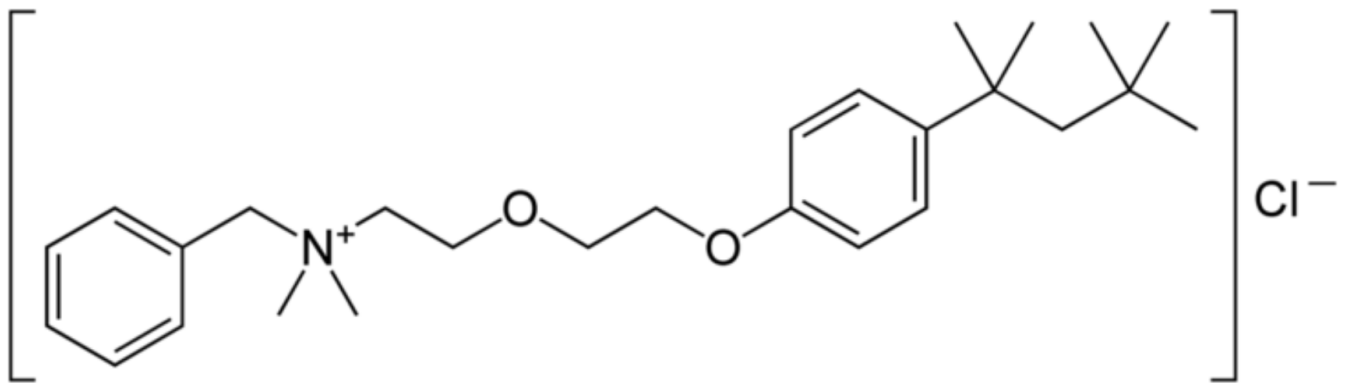
In vitro studies on the fungicidal activity of ketoconazole against samples of filamentous fungi and yeast isolated from animals have been varied. Concentrations from 10mg / m have fungicide effect on *Trichophyton verrucosum* and *Malassezia pachydermatis*, while the yeast phase of *Sporothrix schenckii* in *Cryptococcus neoformans*, *Histoplasma capsulatum* in and *Blastomyces dermatitidis* are needed to

Coccidioides immitis 20mg/me 50mg /. The concentration of ketoconazole 50mg / m on *Trichophyton mentagrophytes* and *Microsporum canis* was moderately fungicidal. Regardless of the tested concentrations of ketoconazole (10 to 1,000 mg / m), the best effects strongly fungistatic and fungicidal were obtained respectively equinum against the *Trichophyton* and *Microsporum nanum*, whereas for *Aspergillus fumigatus*, *Candida albicans*, *Candida tropicalis* and *Candida albicans* activity of the drug was low (Gabal, 1986). The

minimum inhibitory concentration (MIC) averaged for samples of *Malassezia pachydermatis* isolated from the ear canal of dogs was 0.019 mg / m and 0.012 mg / m for samples isolated from the skin (Coutinho, 1997). Ketoconazole had the best in vitro activity against *M. pachydermatis*, when compared to other antifungal agents (clotrimazole, miconazole, nystatin and pimaricina) with a MIC at a concentration of 0.02 mg / m reaching 11 samples including a standard strain of 42 samples studied (Uchida et al., 1990). For *M. pachydermatis* in vitro resistance to ketoconazole has been low, ranging between 0 and 6.7% (UCHIDA et al. 1990; Coutinho, 1997).

Benzethonium Chloride

Benzethonium chloride, N-Benzyl-N,N-dimethyl-2-{2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethoxy}ethanaminium chloride, is a synthetic quaternary ammonium salt. It has surfactant, antiseptic, and anti-infective properties, and it is used as a topical antimicrobial agent.



In addition to its highly effective antimicrobial activity, benzethonium chloride contains a positively charged nitrogen atom covalently bonded to four carbon atoms. This positive charge attracts it to the skin and hair. This contributes to a soft, powdery after feel on the skin and hair, as well as long-lasting persistent activity against microorganisms.

Disinfectant Action

Benzethonium chloride is a cationic surfactant, low surface tension, which act by increasing the permeability of cell membranes of microorganisms, allowing hydration of the cells and its implosion with loss of nitrogen and potassium, and inactivation of the bacterial enzyme system.

Ketoconazole and Benzethonium Chloride Safety

Both ketoconazole and benzethonium chloride are very safe at this concentration for topical use in dogs and cats. However, like any other active ingredient used topically, both ketoconazole and benzethonium chloride can result in a local allergic reaction. In these cases, it is recommended to stop using the shampoo and wash



CLINICAL AND SCIENTIFIC DOCUMENTATION SUBSTANTIATING THE SAFETY AND EFFICACY OF ANTISEPTIC & ANTIFUNGAL SHAMPOO

the region immediately with plenty of water to remove excess product. If necessary, contact your Veterinarian.

References:

1. GABAL, M.A. Antifungal activity of ketoconazole with emphasis on zoophilic fungal pathogens. Am J Vet Res, v.47, p.229-1234, 1986.
2. MORIELLO, K.A. Ketoconazole: clinical pharmacologic and therapeutic recommendations. J Am Vet Med Assoc, v.188, p.303, 1986.
3. NOXON, J.O.; DIGILIO, K.; SCHMID, T.D.A. Disseminated histoplasmosis in a cat: successful treatment with ketoconazole. J Am Vet Med Assoc, v.181, n.8, p.817-820, 1982.
4. RICHARDSON, M.D.; WARNOCK, D.W. Fungal infection –Diagnosis and management. London : Blackwell, 1993. Cap.3: Antifungal drugs: 17-43.
5. STAUB, I.; BERGOLD, A.M. Determination of ketoconazole in shampoo by high performance liquid chromatography. Acta Farm. Bonaerense, v. 23, n. 3, p. 387-390, 2004.
6. STAUB, I.; SCHAPOVAL, E.E.S.; BERGOLD, A.M. Microbiological assay of ketoconazole in shampoo. Int. J. Pharm., v. 292, p. 195- 199, 2005.
7. STEWART, G.A., PHILPOT, W.W. Efficiency of a quaternary ammonium teat dip for preventive intramammary infections. J. Dairy Sci., v.65, p.878-80, 1982.

THE ART OF SHAMPOOS IN VETERINARY DERMATOLOGY: TREATMENT AND PREVENTION STRATEGIES

Topical therapy (locally acting) is extremely important in the management of many dermatological conditions. Several formulations are available for the prescribing veterinary surgeon: shampoo, lotion, spray, ointment, cream, milk and gel. Choice varies according to the case and must take into account the nature and extent of the lesions, animal's temperament and owner time available. Shampoos are nowadays widely used by veterinary dermatologists.

I. Shampoos: What are they, how do they work, how to use them?

A shampoo is an aqueous solution, with added surfactant(s), cleansing agents and various other therapeutic and/or cosmetic agents. Cleaning agents rid the skin surface of debris and help clear the apical pole of hair follicles (1).

Washing the skin with a topical cleanser should always precede actual topical therapy. Ideally, a shampoo possessing both cleansing and therapeutical properties should be applied twice.

A shampoo can be used in a limited area (eg chin, feet, dorsolumbar, ventral areas), as in humans for the hairy skin, or more commonly all over the body surface of a dog or a cat for treating generalized conditions.

The mechanical effect (elimination of scales and crusts) of the bath is beneficial in all cases. Water rehydrates the stratum corneum although this effect is temporary in the absence of moisturisers.

At the second application, the shampoo must be left on for several minutes, to allow the active ingredients to be properly absorbed and reach adequate levels in the deep cellular layers. This length of time varies between 5 and 15 minutes according to choice of product, concentration, type of base, and the skin condition. The skin should then be rinsed thoroughly, for at least 5 minutes, to prevent irritation and to enable the skin to become adequately hydrated.

The shampoo may be applied several times a week for 2 weeks. The frequency is then reduced to give the longest interval over which treatment is still effective, usually about 1 to 2 weeks.

II. Efficacy of shampoo therapy Clinical improvement is the main criterion to evaluate the efficacy of shampoos (see below for efficacy in specific indications) (2). Their use has increased greatly in North America over the past 25 years, but they have been slow to gain acceptance in Europe (3). However, they are now



CLINICAL AND SCIENTIFIC DOCUMENTATION SUBSTANTIATING THE SAFETY AND EFFICACY OF ANTISEPTIC & ANTIFUNGAL SHAMPOO

widely used in the old continent, despite the fact that they were considered as contraindicated and even harmful by many teachers in veterinary schools in the 60's, who recommended "not to wash dogs". This was a mistake and has probably delayed considerably the use of medicated shampoos, which is now considered as being indispensable by the veterinary dermatology community.

The efficacy of shampoos on skin hydration, the surface lipid film and stratum corneum (interesting in case of keratoseborrheic disorders) can be evaluated objectively using a variety of techniques : transepidermal water loss (TEWL) measurement, corneocyte counts, measurement of corneal layer thickness, stripping, chemical analysis of lipid film, water content measurement, surface biopsies and corneometry (4-8). In one study (7) corneometry, but not TEWL measurement, was found to give reproducible results. In another study, results from TEWL measurement, corneometry and sebometry were not reproducible and these procedures were therefore deemed to be useless in evaluating effects of topical treatments in the dog (8). Electron microscopy could perhaps be useful (9).

In recent years, there has been considerable progress in improving topical formulations, especially in prolonging the action of active ingredients applied to the skin. Microencapsulation (multilamellar microvesicles, liposomes, spherulites) increases bioavailability of therapeutic agents and promotes immediate and residual moisturising properties. Active agents are released from liposomes by membrane rupture. Spherulite surfactants are amphiphilic (two antagonistic extremities - one hydrophilic, the other hydrophobic). They unit to form lamellar phases and are arranged in concentric layers according to a specific manufacturing process. They are multilamellar, each membrane acting as a diffusion barrier to reduce loss of active ingredients to the external environment. They can act as a vehicle for a great number of active agents, hydrophilic or hydrophobic (lipophilic), released continuously and progressively at the surface of hairs and skin. This surfactant formulation is very useful in dermatology because it allows hydrophilic, active ingredients access to an oily environment and conversely hydrophobic, active ingredients access to an aquatic medium. The type of surfactant varies. In some cases (cationic surfactants), their charge is positive and spherulites attach preferentially to hairs and skin, whilst in other cases (non- ionic surfactants), the charge is neutral, allowing spherulites to penetrate the deeper skin layers. A study has demonstrated that non-ionic spherulites can penetrate the epidermis, hair follicles, sebaceous glands and dermis (10). The presence of chitosanide reinforces the cationic phase and, by creating a film sheath over the hair, promotes excellent moisturising properties.

A new veterinary formulation (micro-emulsion), with excellent solubility of active ingredients, has recently become available.

III. The use of shampoos in keratoseborrheic disorders (11) 1 Keratomodulating agents

Keratomodulating agents work in two different ways :

- restoration of normal keratinocyte multiplication and keratinisation. A cytostatic effect is probably exerted on basal cells, thereby reducing their rate of division. Agents working in this way are called keratoplastic (keratoregulating) ;
- elimination of excess corneal layer production, either by increasing desquamation or by reducing intercellular cohesion. Agents that work in this way are called keratolytic. There are several types of keratomodulating agents.

There are also antiseborrheic agents which act at the level of the sebaceous gland and its duct (1,12,13). Salicylic acid is a keratolytic agent. It causes a reduction in skin pH which leads to an increase in:

- 1) the amount of water that keratin is able to absorb. Stratum corneum hydration is therefore also increased ;
- 2) desquamation, via direct effect on intercellular cement.



CLINICAL AND SCIENTIFIC DOCUMENTATION SUBSTANTIATING THE SAFETY AND EFFICACY OF ANTISEPTIC & ANTIFUNGAL SHAMPOO

These actions help soften the corneal layer. Salicylic acid acts synergistically with sulphur, and is often present in small quantities in shampoos. Its efficacy varies with concentration.

Coal tar is a keratoplastic (cytostatic) agent. It reduces nuclear synthesis in the epidermal basal layers (13,14). It is also antiseptic and antipruritic. There are many different sources and varieties of this active agent. Tar is a complex mixture of aromatic hydrocarbons, with many constituents (more than 10,000). It is hard to determine which is (are) responsible for therapeutic effects. Standardisation is therefore difficult, and good quality preparations must be used. Smell and consistency of commercial preparations sometimes make it difficult to use, although deodorised veterinary preparations are now available. Side-effects (e.g. skin drying, discolouration of pale coats and irritation) have been reported with high concentrations (over 3 %) (1). Its use is contraindicated in the cat.

Sulphur is keratolytic. It forms hydrogen sulphide in the corneal layer and has numerous other, mainly antiseborrhoeic, properties (see below). It is also keratoplastic, due to a direct cytostatic effect and possibly because it interacts with epidermal cysteine to form cystine, an important component of the corneal layer (3,12-14). It is gradually being replaced in topical products by other more effective keratomodulating agents with fewer side-effects (e.g. a rebound increase in scaling).

Selenium disulphide is keratolytic and keratoplastic (reduced epidermal turnover and impaired disulphide bridge formation in keratin). It is also antiseborrhoeic (see below) (3,12,13). It too can cause rebound increase in scaling and sometimes skin irritation.

Ammonium lactate has keratoplastic and keratolytic activity. In the management of human seborrhoea, it has been shown to be effective in removing excessive scale by virtue of its keratoplastic activity (15-18). Its mechanisms of action in seborrhoeic disorders have not yet been completely elucidated but it seems to stimulate the living epidermis, correcting defects in keratinocyte multiplication and maturation. This facilitates terminal keratinocyte differentiation, leading to more normal desquamation (19,20). Its properties are useful in seborrhoeic disorders where the ammonium lactate has important moisturising properties (17,18,20). Several clinical studies in man indicate that this substance is very well-tolerated, even when used over prolonged periods (15-19).

2. Antiseborrhoeic agents

Antiseborrhoeic agents inhibit or reduce sebum production by the sebaceous glands, and help clear the ducts.

Sulphur (see above) is a classic antiseborrhoeic agent, but is drying and may trigger a rebound effect. It is also antiseptic. It exerts synergistic activity with salicylic acid. This synergism appears optimal when both substances are incorporated into the shampoo in equal concentrations (21).

Selenium disulphide (see above) is antiseborrhoeic, but also has detergent, irritant and drying effects. It is contraindicated in the cat.

Benzoyl peroxide, in addition to being antibacterial, is antiseborrhoeic, thanks to sebum hydrolysis and reduced sebaceous gland activity. One study showed that 3% benzoyl peroxide shampoos increase transepidermal water loss and decrease skin surface lipid concentration and corneocyte counts (6). Benzoyl peroxide exerts a follicular flushing action which is very useful when treating comedone disorders and/or follicular hyperkeratosis (3,4,13,22). Side effects (irritations, erythematous rash) have been reported especially in concentrations above 5% (4). The skin may also become dry and emollients are therefore



always indicated after using this product.

3. Essential fatty acids Various veterinary shampoos have incorporated essential fatty acids for their softening and moisturising properties. One study has demonstrated that in seborrhoeic dogs, abnormal transepidermal water loss could be corrected by applying linoleic acid (23). Some shampoos contain moisturisers : glycerin, lactic acid and fatty acid polyesters. Moisturisers can be stored in multilamellar structures for prolonged release (spherulites), or mono/oligolamellar bodies (liposomes) to ensure hydration levels are maintained.
4. How to use shampoos in keratoseborrhoeic disorders Certain guidelines are suggested :
 - long-haired dogs with severe seborrhoeic disorders should be clipped. Clipping leads to more effective application and better distribution of the active ingredient ;
 - shampoos should initially be applied 2 to 3 times weekly. With time, frequency of application can gradually be reduced ;
 - cases should be monitored frequently. The therapeutic agent often needs to be changed following the development of side-effects, rebound effects or change in clinical presentation (e.g. transition from greasy seborrhoea to dry seborrhoea).

IV. The use of shampoos in parasitic diseases

Antiparasitic shampoos, ie containing organochlorines, natural pyrethrins or synthetic pyrethroids, are not considered to be as efficacious as antiparasitic rinses and dips (12) and other formulations (sprays, pump-sprays, powders, spot-ons, line-ons, systemic agents), mainly because they are rinsed and cannot act during a sufficient time (2). Scabies, cheyletiellosis, otodectic mange, tick infestation, trombiculosis and pediculosis are relative indications.

Insecticidal shampoos often contain synthetic pyrethroids chosen for their rapid knock-down effect : these are best used as a convenient one-off treatment to rid an animal of a resident flea infestation. As there is usually little or no residual action once the shampoo is rinsed off, the treated animal is immediately vulnerable to reinfestation by host-seeking fleas. Normally, therefore, shampoos have limited application in the long-term management of flea infestation (pulicosis) and flea allergy dermatitis (24). However, a shampoo containing deltamethrin (0.07%) has been shown recently to maintain a > 90 % antifeeding effect during the hour following challenge for one week (25).

Colloidal oatmeal, an antipruritic agent (see below) is added to bioallethrin , a pyrethroid, in a shampoo to decrease inflammation due to the parasitic infestation.

Benzoyl peroxide shampoos are recommended in the treatment of demodicosis because of their degreasing and follicular flushing effect (3,12).

Many parasitic diseases (e g scabies, cheyletiellosis) and flea allergy dermatitis can cause a keratoseborrhoeic disorder and the affected animals will benefit from application of keratomodulating shampoos (3).

V. The use of shampoos in bacterial diseases (pyoderma)

Topical therapy is used in canine pyoderma to reduce the cutaneous bacterial population and antibacterial shampoos also remove tissue debris, allowing direct contact of the active ingredient with the organism and promoting drainage (12).

Limited cases of superficial pyoderma can be treated with shampoos alone, particularly if they are used frequently at the beginning (e g every day), then decreasing the frequency of applications depending on the animal's response. However in most cases systemic antibiotics will be administered to ensure a more prompt response, the shampoo playing a supporting role (3). A common indication for long-term use is in the dog



CLINICAL AND SCIENTIFIC DOCUMENTATION SUBSTANTIATING THE SAFETY AND EFFICACY OF ANTISEPTIC & ANTIFUNGAL SHAMPOO

that is prone to recurrent folliculitis, either idiopathic or eventually secondary to endocrine or allergic skin disease, even though the pruritus due to the allergic skin disease is controlled. In these situations well tolerated antibacterial shampoos may have a prophylactic effect if used regularly i e every one to two weeks(3,12).

In case of deep pyoderma, clipping is preferable before using shampoos (and soaks). This will prevent the formation of a sealing crust and allow the product to contact the lesions (furuncles, ulcers) (12). In such cases, shampoos should be used very frequently at the initiation of treatment.

Agents commonly included in antibacterial shampoos are chlorhexidine, povidone-iodine, benzoyl peroxide and ethyl lactate.

Chlorhexidine (4,26) is a biguanide antiseptic, very effective against most bacteria (Gram + and -), except some Pseudomonas and Serratia strains. It is bactericidal by action on cytoplasmic membrane which causes leak of intracellular components. Concentrations vary in shampoos from 0.5 to 4% (diacetate or digluconate). It has a prophylactic effect due to its remanence (27,28). It is well tolerated.

Povidone-iodine is a iodophore which slowly releases iodine to tissues (4,12). The titratable iodine is usually of the order of 0.2 to 0.4 per cent. It is bactericidal and acts in a few seconds at 0.005 % (2). It has also a prophylactic effect due to its remanence (28). It is relatively drying which can be compensated by emollients in shampoos. It can be irritant and staining (4).

Benzoyl peroxide (see above) is metabolized in the skin to benzoic acid and much of its microbiocidal activity probably derives from the lowered skin pH (3). This disrupts microbial cell membranes (3,4). It is in fact an oxidizing agent, which releases nascent oxygen into the skin and produces a series of chemical reactions resulting in permeability changes and rupture of bacterial membranes (4). It has an excellent prophylactic effect, the best one in a comparative study with chlorhexidine, complexed iodine and triclosan (28). It is generally used in concentrations of 2 to 3 %, which are well tolerated but irritation can occur at higher concentrations (erythema, pruritus and pain) (4). In a clinical study done in 1983 in 30 dogs with folliculitis, 61 % of dogs responded well to a 2.5 % benzoyl peroxide shampoo, without concurrent therapy (29). In a comparative study on superficial pyoderma, 70 % of 10 dogs responded well to a 2.5 % benzoyl peroxide shampoo (30).

Ethyl lactate is hydrolysed in the skin to ethanol and lactic acid, thus lowering the skin pH and acting similarly to benzoyl peroxide (3). It is used in concentration of 10 %, which is rarely followed by undesirable side effects (irritation, erythema, pruritus) (4). In a comparative study to benzoyl peroxide, 90 % of 30 dogs with superficial pyoderma responded well to a 10 % ethyl lactate shampoo (30). In a recent study comparing two groups of 10 dogs with superficial pyoderma, it was shown that utilization of a 10 % ethyl lactate shampoo twice weekly reduces the length of systemic antibiotic needed in canine superficial pyoderma (31).

Other antibacterial agents used in shampoos are hexachlorophene (not much used because of neurotoxicity), hexetidine (only one product) and triclosan (less effective than benzoyl peroxide and chlorhexidine in a comparative study) (28).

In a recent shampoo formulated specifically for canine atopy, piroctone olamine (widely used in human shampoos) has been added for its antibacterial and anti-yeast properties (see below).

VI. The use of shampoos in fungal diseases

Antimycotic shampoos are used as adjunctive therapy for dermatophytosis and Malassezia dermatitis. They limit contagiosity in case of dermatophytosis but are not effective in treating it when used alone (32). Non antifungal shampoos or shampoos with insufficient antifungal properties can disseminate spores (33). However,



CLINICAL AND SCIENTIFIC DOCUMENTATION SUBSTANTIATING THE SAFETY AND EFFICACY OF ANTISEPTIC & ANTIFUNGAL SHAMPOO

keratomodulating shampoos are used before antifungal topical therapy when there is a keratoseborrhoeic disorder and they are then beneficial in removing infected scales and crusts. In an in vitro study a ketoconazole shampoo was effective to inhibit the growth on Dermatophyte Test Medium of *Microsporum canis* from infected hair, but after more applications than antifungal solutions (enilconazole, lime sulfur, 2% chlorhexidine, povidone iodine) (34). In a review, a miconazole shampoo is considered to be as effective as lime sulfur and enilconazole in treating feline dermatophytosis (33). In a recent study a shampoo containing chlorhexidine (2%) and miconazole (2%) was shown to accelerate the clinical cure but not the mycological cure of cats infected with *Microsporum canis* and treated with griseofulvin (35).

Topical therapy is an alternative to systemic treatment in *Malassezia* dermatitis. For extensive lesions antifungal shampoos or lotions are preferable. They can be used with systemic therapy, although there is no formal evidence that the combination is of greater value than systemic treatment alone. Topical therapy alone should not be used as a diagnostic challenge, but it can maintain a remission, thus confirming the diagnosis. Shampoos containing miconazole (2%), chlorhexidine (2 to 4%), a combination of both (2% each), ketoconazole (2%) or a combination of chlorhexidine (2%) and ketoconazole (1%) are the most appropriate (as are rinses such as lime sulfur and enilconazole) (12,36,37). Selenium sulphide shampoos could be less effective (37).

A study has demonstrated the immediate and residual in vivo antifungal effect of a shampoo containing piroctone olamine against *Malassezia pachydermatis* (38).

VII. The use of shampoos in allergic diseases. All shampoos are likely to remove allergens from the skin, which is supposed to be useful in canine atopic dermatitis. They also help to rehydrate dry skin, which is common in dogs with allergic skin disease. In addition, shampoos with an antipruritic effect can improve the condition of allergic dogs, provided they are used frequently (e.g. twice a week, at least at initiation of therapy). Antipruritic shampoos are considered generally as adjunctive treatments. They are rarely affective as the sole therapy (3,12).

Antipruritic shampoos contain 1% hydrocortisone, 0.01% fluocinolone, 2% diphenhydramine, 1% pramoxine or colloidal oatmeal. A clinical study has demonstrated that shampoos and rinses containing the local anesthetic, pramoxime, are useful (39). The topical fluocinolone shampoos have been shown not to be systematically absorbed in the dog. Controlled studies on efficacy of antipruritic shampoos are lacking (12).

A shampoo specifically designed for canine atopic dermatitis has been recently developed. It contains linoleic acid, mono and oligosaccharides, vitamine E, and piroctone olamine. Linoleic acid can help in restauring the barrier function of the skin (see above) (23), thus limiting the transcutaneous penetration of allergens. In effect, it has been demonstrated that the stratum corneum intercellular lipids are altered in atopic dogs (9). Mono and oligosaccharides are immunomodulator agents, which can inhibit the secretion of proinflammatory cytokines (such as TNF) and limit the expression of membrane molecules (such ICAM 1). In vitro studies have been done in man (40) and dog (41). Vitamine E is an antioxidant, stabilizes lysosomes, reduces prostaglandin E2 (PGE2) synthesis, and increases interleukin 2 (IL-2) production with resultant anti-inflammatory and immunostimulatory effects (12). Piroctone olamine is an antiseptic agent active on Gram + and Gram - bacteria, dermatophytes and yeast. It is much used in topical formulations in human dermatology against proliferation of *Malassezia furfur*. The concept of this shampoo is promising since its goal is to provide a therapeutic response to defects potentially occurring in canine atopic dermatitis. Controlled trials are needed to document the clinical efficacy of this product in atopic dogs.

VIII. Moisturisers

In every skin disorders, and in particular with dry seborrhoea, there is scope for increasing the humidity of the animal's skin, after shampooing, with a moisturiser. It has been demonstrated that skin hydration is less in dogs with scaling than in normal dogs (42).



CLINICAL AND SCIENTIFIC DOCUMENTATION SUBSTANTIATING THE SAFETY AND EFFICACY OF ANTISEPTIC & ANTIFUNGAL SHAMPOO

Moisturisers lubricate, rehydrate and soften the skin. In French, they are all, incorrectly, lumped together as emollients. Moisturisers actually consist of true emollients, emulsifiers/emollients, occlusive dressings and rehydrating agents.

They restore an artificial superficial skin film. Diluted in water, they can be massaged into the skin or applied as a lotion. Undiluted, they may be sprayed on after a shampoo. They should not be rinsed off. In Europe only emollients and rehydrating agents are found in veterinary products (an emulsifier/emollient combination exists in North America). Occlusive dressings are neither used nor marketed in the veterinary field due to risk of maceration.

Emollients are composed principally of fatty acid polyesters, vegetable oils, mineral oils (no veterinary formulations available) and lanolin.

Lipid emollients, containing lanolin alcohols, liquid paraffin or mineral oils, were borrowed from human dermatology and are now rarely used. Used as an emulsion in tepid water, they do improve coat condition, but also have a greasing effect, a definite disadvantage. One veterinary lipid emollient containing fatty acid polyesters is marketed in France. Local application of essential fatty acids has also been proposed to soften and rehydrate the skin, and reduce transcutaneous water loss (23). No major occlusive effect is involved, and the effects are probably brought about by the incorporation of essential fatty acids (especially linoleic acid) into stratum corneum ceramides.

Non-lipid emollients have rehydrating and softening properties. They reduce smell and improve coat appearance without the greasing effect. The high molecular weight of their active ingredients and their hygroscopic nature make them effective surface-protecting therapeutic agents. Examples include lactic acid, glycerin, propylene glycol, urea and chitosanide.

Active agents can be combined with moisturisers : colloidal oatmeal extracts and aloe vera for antipruritic activity, and coal tar for keratolytic and keratoplastic activity.

A lotion has been developed to complement the shampoo specifically designed for canine atopic dermatitis. In a fluid emulsion excipient contains mono and oligosaccharides (free and in spherulites), vitamine E and linoleic acid. This lotion can be used in between shampoos.

IX. Conclusion

Treatment and prevention strategies in veterinary dermatology include often the use of medicated shampoos. The therapeutic plan should be defined on short and long term basis to obtain the best results, to cope with owners compliance and to limit potential side effects (43). Even with the tremendous recent progresses in companion animal dermatology, there is still a certain amount of art as well as science in devising the optimum topical therapy (3).

References 1 Legeay Y (1993) Topiques en dermatologie. Encyclopédie Vétérinaire, Paris, 0700, 7p. 2 Curtis CF (1998) Use and abuse of topical dermatological therapy in dogs and cats. Part 1- shampoo therapy. In Practice, 244-251. 3 Halliwell REW (1991) Rational use of shampoos in veterinary dermatology. J Small Anim Pract 32 : 401-407. 4 Guaguère E (1996) Topical treatment of canine and feline pyoderma. Vet Dermatol 7: 145- 151. View pictures View other presentations 5 Campbell KJ, Schaeffer DJ (1993) Effects of four veterinary shampoos on transepidermal water losses, hydration of the stratum corneum, skin surface lipid concentration, skin surface pH and corneocyte count in dogs. In: Proceedings of the ninth annual meeting of the American Academy of Veterinary Dermatology and American College of Veterinary Dermatology, San Diego, 96-97. 6 Campbell KJ et al (1994) Effects of four antiseborrheic shampoos on transepidermal water losses, hydration of the stratum corneum, skin surface lipid concentration, skin surface pH and corneocyte count in dogs. In: Proceedings of the tenth annual meeting of the American Academy of Veterinary Dermatology and American College of Veterinary Dermatology, Charleston, 85. 7 Beco L, Fontaine J (2000) Cornéométrie et perte d'eau transépidermique : validation des techniques chez des chiens sains. Ann Méd Vét, 144 : 329-333. 8 Groux D, Bensignor E (2000) Skin characteristics measured by trans-epidermal water



CLINICAL AND SCIENTIFIC DOCUMENTATION SUBSTANTIATING THE SAFETY AND EFFICACY OF ANTISEPTIC & ANTIFUNGAL SHAMPOO

loss, corneometry and sebometry are not valuable tools to evaluate the effects of topical treatments in dogs. *Vet Dermatol*, 11(Suppl.1) : 60. 9 Inman AO, Olivry TO, Dunston SM, Monteiro-Riviere NA, Gatto H (2001) Electron microscopic observations of the stratum corneum intercellular lipids in normal and atopic dogs. *Vet Pathol* 38 : 720-723. 10 Barthe N, Jasmin P, Brouillaud B, Guinez C, Coulon P, Gatto H (1999) Assessment of the Bio-Distribution of Non-Ionic Spherulites in Dog Skin. *Proceedings of the 16th Annual Congress of the European Society of Veterinary Dermatology and European College of Veterinary Dermatology*, Helsinki, 156. 11 Carlotti DN, Bensignor E (2002) Management of keratoseborrheic disorders. *Eur J Comp Anim Pract*, 12 : 123-133. 12 Scott DW, Miller WH, Griffin CE (2001) *Muller and Kirk's Small Animal Dermatology*, 6th edition, WB Saunders Company, Philadelphia. 13 Kwochka KW (1993)

Symptomatic Topical Therapy of Scaling Disorders. In: *Current Veterinary Dermatology* (Griffin CE, Kwochka KW, Mac Donald JM, Eds) Mosby Year Book, St Louis, 191-202. 14 Kietzman M et al (1990) Effects of sulphur and coaltar in epidermal metabolism. In: *Advances in Veterinary Dermatology I* (Von Tscharnner C, Halliwell REW Eds), Bailliere Tindall, London, 460-461. 15 Rogers RS et al (1989) Comparative efficacy of 12% ammonium lactate lotion and 5% lactic acid lotion in the treatment of moderate to severe xerosis. *J Am Acad Dermatol* 21: 714- 716. 16 Klaus MV et al (1990) Evaluation of ammonium lactate in the treatment of seborrheic keratoses. *J Am Acad Dermatol* 22 : 199-203. View pictures View other presentations 17 Jennings MB et al (1998) Comparison of salicylic acid and urea versus ammonium lactate for the treatment of foot xerosis. A randomized, double-blind clinical study. *J Am Podiatr Med Assoc* 88 : 332-336. 18 Uy JJ et al (1999) Ammonium lactate 12% lotion versus a liposome-based moisturizing lotion for plantar xerosis. A double-blind comparison study. *J Am Podiatr Med Assoc* 89 : 502-505. 19 Lavker RM et al (1992) Effects of topical ammonium lactate on cutaneous atrophy from a potent topical corticosteroid. *J Am Acad Dermatol* 26 : 535-544. 20 Vilaplana J et al (1992) Clinical and non-invasive evaluation of 12% ammonium lactate emulsion for the treatment of dry skin in atopic and non- atopic subjects. *Acta Derm Venereol* 72 : 28-33. 21 Leyden JJ (1987) Effects of sulfur and salicylic acid in a shampoo base in the treatment of dandruff: a double-blind study using corneocyte counts and clinical grading. *Acta Derm Venereol*, 39: 557. 22 Ihrke PJ (1980) Topical therapy: specific topical pharmacologic agents - Dermatologic therapy (part II) *Comp Cont Educ Prat Vet* 11 : 156-164. 23 Campbell KJ, Kirkwood AR (1993) Effects of topical oils on TEWL in dogs with seborrhea sicca. In : *Adv. Vet. Derm. II*, Eds Ihrke PJ, Mason IS, White SD, Pergamon Press, Oxford, 157-162. 24 Carlotti DN, Jacobs DE (2000) Therapy, control and prevention of flea allergy dermatitis in dogs and cats. *Vet Dermatol* 11 : 83-98. 25 Franc M, Cadiergues MC (1998) Activité anti-gorgement d'un shampoing à 0.07% de deltaméthrine sur les puces du chien, *Ctenocephalides Felis*. *Rev Méd Vét* 149 : 791-794. 26 Carlotti DN, Maffart P (1996) La chlorhexidine, revue bibliographique. *Prat Méd Chir Anim Comp* 31 : 553-563. 27 Campbell KJ et al (1995) Effects of four antibacterial soaps/shampoos on surface bacteria of the skin of dogs. In: *Proceedings of the eleventh annual meeting of the American Academy of Veterinary Dermatology and American College of Veterinary Dermatology*, Santa Fe, 43- 44. 28 Kwochka AK, Kowalski J (1991) Prophylactic efficacy of four antibacterial shampoos against *Staphylococcus intermedius* in dogs. *Am J Vet Res*, 52 : 115-118. 29 Lloyd DH, Reys-Brion A (1984) Le Peroxyde de benzoyle : efficacité clinique et bactériologique dans le traitement des pyodermes chroniques. *Prat Méd Chir Anim Comp* 19 : 445-449. 30 Ascher F, Maynard L, Laurent J, Goubet B (1990) Controlled trial of ethyl lactate and benzoyl peroxide shampoos in the management of canine surface pyoderma and superficial pyoderma. In : *Advances in Veterinary Dermatology Volume 1*, Eds Von Tscharnner C, View pictures View other presentations Halliwell REW, Bailliére Tindall, London, 375-382. 31 De Jaham C (2002) Usefulness of an ethyl lactate shampoo in conjunction with systemic antibiotics in the treatment of canine generalized superficial pyoderma : a controlled clinical study. In : *Proceedings of the 18th annual congress of the European Society of Veterinary Dermatology and European College of Veterinary Dermatology*, Nice, 199. 32 DeBoer DJ, Moriello KA (1995) Inability of two topical treatments to influence the course of experimentally induced dermatophytosis in cats. *J Am Vet Med Assoc* 207 : 52-57. 33

Moriello KA, DeBoer DJ (1995) Feline dermatophytosis. Recent advances and recommendations for therapy. *Vet Clin. North Am Small Anim Pract* 25 : 901-921. 34 White-Weithers N, Medleau L (1995) Evaluation of topical therapies for the treatment of dermatophytosis in dogs and cats. *J Am Anim Hosp Assoc* 31 : 250-253. 35 Paterson S (1999) Miconazole/chlorhexidine shampoo as an adjunct to systemic therapy in controlling dermatophytosis in cats. *J Small Anim Pract* 40 : 163-166. 36 Mason KV (1993) Cutaneous Malassezia. In : *Current Veterinary Dermatology*, Eds Griffin CE, Kwochka KW, Mac Donald JW, Mosby Year Book, Saint-Louis, 44-48. 37 Bond R, Rose JF, Ellis JW, Lloyd DH (1995) Comparison of two shampoos for treatment of Malassezia pachydermatis-associated seborrheic dermatitis in basset hounds. *J Small Anim Pract* 36 : 99-104. 38 Bourdeau P, Blumstein P, Ibish C, Gardey L., Jasmin P, Gatto H (1999) Antifungal activity of a piroctone shampoo against Malassezia populations after a single treatment in the dog. In *Proceedings 16th Annual Congress of the European Society of Veterinary Dermatology and European College of Veterinary Dermatology*, Helsinki, 155. 39 Scott W et al (2000) A clinical study of the efficacy of two commercial veterinary pramoxine cream rinses in the management of pruritus in atopic dogs. *Canine Pract* 25 : 15- 18. 40 Palacio S, Viac J, Vinche A, Huband JC, Gatto H, Schmitt D (1997) Suppressive effects of monosaccharides on ICAM-1/ CD54 expression in human keratinocytes. *Arch Dermatol Res* 289 : 234- 237. 41 Cadiot C, Ibisch C, Bourdeau P, Gatto H (2000) In vitro assay for detection of canine keratinocyte activation : preliminary results for pharmacological tests of activation/regulation. *Vet Dermatol* 11 (Suppl 1) : 58. 42 Chesney CJ (1998) The intimate envelope: water and the skin. In : *Advances in Veterinary Dermatology 3rd edition*, Eds Kwochka KW, Willemse T, Von Tscharnner C, Butterworth Heinemann, Oxford, 47-56. 43 Koch HJ (1996) Shampoo therapy in veterinary dermatology. *Proceeding of the Third World Congress of Veterinary Dermatology*, Edinburgh, 88-90. D.N. CARLOTTI, Dip ECVD