International Congress of the Italian Association of Companion Animal Veterinarians

27 - 29 May, 2011
Rimini, Italy

Next Congress :

SCIVAC International Congress
Mar. 8-10, 2013 - Pisa, Italy

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INTRODUCTION
Otitis externa is one of the most prevalent diagnoses in canine practice. Small inflammatory changes in the fragile microclimate of the skin in the external ear allow abnormal proliferation of commensal bacteria (*Staphylococcus pseudintermedius*) and yeast (*Malassezia pachydermatis*) or opportunistic invaders (e.g. *Pseudomonas aeruginosa*). This perpetuates inflammation and may eventually lead to significant proliferative pathologic changes. Perpetuating factors make resolution of otitis externa a significant challenge.

TOPICAL TREATMENT
The majority of cases of otitis externa can be treated successfully with topical medication administered into a clean, dry external ear canal. These medications usually contain an antibiotic, antifungal and generally also a glucocorticoid (GC) in an appropriate vehicle. GCs are included to reduce inflammation allowing restoration of the normal environment of the ear canal. Broad-spectrum antibiotic and antifungal agents are included to eliminate the bacteria and yeast associated with otitis externa. The vehicle should ideally allow the active ingredients access to all parts of the ear canal, and provide prolonged contact with its epithelial lining.

GCs enter cells and complex with specific glucocorticoid receptors (GCR) in the cytoplasm. The GC-GCR complex moves to the nucleus and binds to glucocorticoid response elements, leading to transcription and production of certain proteins that are known to have anti-inflammatory actions, e.g. lipocortin-1. GC inhibit both the early and late (healing, repair, and chronic proliferative reactions) stages of inflammation. Finally, GC decrease glandular secretions from the epithelial glands of the ear canal, making the ear canals a less favorable environment for bacteria and yeast to multiply.

The potency of GC following topical application depends on agent, concentration, salt (lipid solubility) and formulation. Potency is directly related to the agonistic GCR affinity and retention in the target tissue but is also concentration related. Formulations that are oil-based, such as ointments and suspensions, are more potent than formulations that contain more water, such as creams, gels and solutions. Suspensions are generally favored by veterinarians because they provide good contact with, and distribution within, the ear canal and can easily be applied as drops.

NOVEL AGENTS
A novel ototopical suspension containing the glucocorticoid mometasone furoate monohydrate (0.1%), the fluoroquinolone antibiotic orbifloxacin (1%) and the triazole antifungal posaconazole (0.1%), (POSATEX®, Intervet/Schering-Plough Animal Health) has been developed for veterinary use.

Mometasone furoate (MF) is a synthetic GC with high topical potency. It has a high affinity for and a long half-life at the GCR. MF is capable of inhibiting pro-inflammatory mediators at very low concentrations *in vitro* and *in animal models*, where its potency has been shown to increase following repeated topical application, as well as in dogs with otitis externa. Only very low amounts of MF are found in plasma following ototopical application. MF is metabolized extensively and its metabolites are excreted in feces. There were no clinical signs or marked increases in liver enzyme activity following ototopical application of MF (*as POSATEX*) at one-, three- and five-times the recommended treatment dose for 21 days in healthy Beagle dogs. Although there was a slight decrease in resting serum cortisol concentration after 21 days in the highest dose group, these dogs could still respond well to ACTH stimulation. In addition, MF has been shown to have a good margin of adrenal safety following application to dogs with otitis externa.

Orbifloxacin is a fluoroquinolone with a broad spectrum of concentration-dependent bactericidal activity. It is particularly well suited to treat the bacterial pathogens and secondary invaders typically encountered in canine otitis externa. Fluoroquinolones selectively inhibit bacterial nucleic acid synthesis by binding topoisomerase IV type II in Gram-positive bacteria and to the A subunits of bacterial DNA gyrase in Gram-negative bacteria, disrupting the spatial arrangements of bacterial DNA, leading to rapid cell death. Orbifloxacin has minimum inhibitory concentration (MIC) ranges of 0.25-2 μg/ml (*MIC*<sub>90</sub> 1 μg/ml) for coagulase-pos-
itive staphylococci, 2-16 μg/mL for *Pseudomonas aerugi-
osa*, 0.016-0.12 μg/mL for *E. coli*, and 1-8 μg/mL for *Ente-
rococcus faecalis*. The Clinical and Laboratory Standards
Institute (CLSI) breakpoints for antimicrobial disk and dilu-
tion susceptibility tests for orbifloxacin are susceptible
≤1 μg/mL, intermediate 2-4 μg/mL and resistant ≥8 μg/mL.
Orbifloxacin is absorbed slowly and moderately following
ototopical application and is excreted predominantly
unchanged, mainly in urine. The concentrations obtained
are unlikely to result in systemic exposure of any toxicological
significance. The clinical efficacy of fluoroquinolones can
be predicted using pharmacokinetic/pharmacodynamic
(PK/PD) surrogates, namely the ratio of the maximum con-
centration (Cmax) to MIC of around 8 to 12 and/or the area
under the curve (AUC) to MIC of around 35 to 125 hours.
The “mutant selection window” hypothesis postulates that
resistance should develop only rarely when drug concentra-
tions exceed the so-called mutant prevention concentration
(MPC), which approximates to the MIC of the least suscepti-
able mutant in a colony. Maintenance of concentrations
above the MPC throughout the dosing interval prevents
resistant mutant selection. Ototopical application of orb-
ifloxacin (as POSATEX, 8.55 mg/mL or 267 μg/drop)
establishes and maintains orbifloxacin concentrations at the
site of infection that greatly exceed both MIC and MPC,
even after potential dilution by exudate.

Posaconazole is a novel triazole with a broad spectrum of
activity. Azoles prevent the synthesis of a major component
of fungal plasma membranes, by inhibiting the cytochrome
P-450-dependent enzyme 14α-demethylase (14-sterol
demethylase or CYP51A1) that is involved in ergosterol
biosynthesis in yeasts and molds.

This leads to the build up of toxic concentrations of
metabolites, which disrupt both the cell membrane and
organelles and leads to inhibition of fungal growth and fun-
gal cell death. Posaconazole has excellent *in vitro* activity
against a broad spectrum of fungal pathogens, and has been
shown to be at least ten-times more effective than micona-
zole and clotrimazole against canine *Malassezia* sp. iso-
lates. It is absorbed slowly and moderately after ototopi-
cal application, with the metabolites excreted principally
in feces. Triazoles such as posaconazole have a greater affini-
ty for fungal rather than mammalian cytochrome P-450
enzymes than other azoles, contributing to their improved
safety profile.

**FIELD EFFECTIVENESS AND SAFETY**

A positive-controlled clinical field study was conducted
in first-opinion small animal practices in France, Belgium
and Germany to examine the field effectiveness and safety
of POSATEX in client-owned dogs with uni- (48%) or
bilateral (52%) otitis externa. Dogs representing 52 differ-
ent pure breeds and 31 mixed or unknown breeds (aged 0.3
to 14.3 years and weighing 3.2 to 68.0 kg), that were pre-
sented with clinical signs of otitis externa associated with
both bacterial and yeast infections were included; around
one-half of the cases were newly diagnosed with otitis
externa. Dogs that had recently been administered ototopi-
al (5 days), systemic antimicrobial (7 days) or systemic
corticosteroid (4 weeks) treatment, as well as dogs with ear
canal obstruction, ruptured tympanic membrane(s) or
owned by clinic staff were excluded. Before treatment,
physical and otoscopic examinations were carried out and
odor, discomfort and/or swelling of the external ear canal,
pinnal erythema, and exudate were awarded a score using
numerical rating scales. In addition, specimens were col-
clected for cytology and culture. The ear canal was then
cleaned with physiologic saline or water. Dogs were allo-
cated randomly to two treatment groups with the investiga-
tor blinded to treatment. Group 1 (n = 100) was adminis-
tered the test product once daily for 7 days. Group 2 (n =
102) was administered a commercially available positive
control product (Surolan<sup>®</sup>, Janssen Animal Health) twice
daily according to the manufacturer’s recommended treat-
dment dose for 7 days. Effectiveness and safety were evalu-
ated on day 8 using physical and otoscopic examinations
and cytology. For pivotal clinical variables the groups were
compared using the Stratified Cochran-Mantel-Haenszel
Rank Sum Test, stratified by site and by the Wilcoxon-
Mann-Whitney Exact Rank Sum. For non-pivotal vari-
able, the groups were compared using Cochran-Mantel-
Haenszel Chi Square Row Means Scores, stratified by site.
Statistical significance was declared when p <0.05.

*Malassezia pachydermatis* was observed in 84% of cases
and bacteria (predominantly *Staphylococcus pseudinter-
medius*) were cultured from 62% of cases at inclusion.
Treatment was successful in 94.4% of dogs from Group 1
and 94.3% of dogs from Group 2 (90% CI of difference
between treatments -5.98% to 6.20%). The clinical cure
rate was 83.6% in Group 1 and 68.3% in Group 2. The sub-
jective clinical scores for odor, swelling, pinnal erythema
and exudate improved with treatment in both groups (p
>0.05). There was a significantly greater improvement in
discomfort (pivotal variable) in Group 1 compared to
Group 2 (p = 0.0029). The vast majority of dogs had no
hearing deficit either before (94.9%) or following (98.7%)
treatment. The investigator overall outcome evaluation
(non-pivotal variable) was significantly better in Group 1
than in Group 2 (p = 0.001). Five adverse events (three in
dogs from Group 1 and two in dogs from Group 2) were
reported during the study.

The significantly greater improvement in discomfort in
Group 1 was presumed to be due to the enhanced topical
potency of MF and likely led to the better overall evaluation
of this product.

**CONCLUSIONS**

POSATEX is intended as a treatment for otitis externa in
dogs associated with susceptible strains of yeast (*Malassezia
pachydermatis*) and bacteria.

It has been demonstrated to be both safe and effective
in the treatment of canine otitis externa associated with yeast
(*Malassezia pachydermatis*) and bacteria when administered
once daily for 7 days.
REFERENCES


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