Otitis topical and systemic

Craig E. Griffin
DVM, Dipl ACVD, California, USA

Topical active ingredients most often incorporated into otic medications are selected for cleaning, drying, and anti-inflammatory or anti-microbial properties. Parasiticidal agents are sometimes included, however they are often unnecessary. Vehicles and dispersion agents are also important in otic topicals.

Topical glucocorticoids are valuable in most cases of otitis externa even when infection is present. Glucocorticoids have antipruritic, anti-inflammatory effects and decrease exudation and swelling. In addition they cause sebaceous atrophy and decrease glandular secretions. Glucocorticoids may reduce scarring and proliferative changes, which helps to promote drainage and ventilation. There are many different types and potencies of topical glucocorticoids available. It is best to choose several products of different potencies and become familiar with them. The more common active ingredients found in veterinary products are, from generally the weakest to more potent, 1% hydrocortisone, 0.1% triamcinolone, 0.1% dexamethasone, 0.1% betamethasone and 0.1% fluocinolone acetonide and mometasone furoate. The 0.1% products listed have been shown to cause adrenal suppression in normal dogs. Dexamethasone at 0.01% does not. (Aniya and Griffin 2007) Dexamethasone sodium phosphate 4 mg/ml actually contains 3 mg of dexamethasone. This is used to make a variety of ear products in the clinic. Most commonly I make products with 0.1% which is 33% of the final product being the dexamethasone sodium phosphate or 0.066% which is 25% of the final mix being the dexamethasone sodium phosphate. My low strength for long term control of allergic otitis is 0.01% which is 1 cc of dexamethasone sodium phosphate with 29 cc of other components, most often 1% miconazole lotion.

Antimicrobial agents include disinfectants, antibiotics and antifungal (yeast) agents. Disinfectants and/or drying agents should be used after the ear is cleaned and relatively dry. They are also used to help prevent swimmers ear, for odor control and to control secondary infections and treat some difficult cases of resistant microbes such as Pseudomonas sp. Many, though not all, of the disinfectants have been shown to have antifungal activity including acetic/boric acid products, chlorhexidine, and silver sulfadiazine. In many cases disinfectants are used alone or in conjunction with antibiotic containing topical to manage many secondary infections. Disinfectants have the advantage of not inducing resistance and are often less expensive. Acetic acid has been shown to be very effective in the treatment of otitis externa in humans. It is believed that its activity is not completely due to the pH because other acidic products are not as effective in killing Pseudomonas and Staphylococcus. It is possible to get a disinfectant effect just by lowering the pH of the ear canal. Advanced pHormula™ Ear Cleanser (Evisco pharmaceuticals) uses novel technology to and citric acid and sodium citrate to maintain the pH of the ear canal below 5 for 18 hours. Another study evaluated 2.5% lactic acid and 0.1% salicylic acid in propylene glycol (Epi-Otic®, Virbac) showing efficacy in 67.7% of clinical cases (Cole, Kwochka et al. 2003). Acetic acid is effective against Pseudomonas, with a 2% solution being lethal within one minute of contact (Thorp, Kruger et al. 1998). White vinegar is generally about 5% acetic acid and it has been recommended as an ear wash when diluted to 2.5% by mixing it in equal amounts with water or 25% water, 25% isopropyl alcohol and 50% white vinegar. Combinations with 2% boric and 2% acetic acid are available commercially. (Malacet, Dermojet® and Oticotic solution, Vedco) Aluminum acetate (Burow’s solution) has also been shown effective for many ear pathogens and as effective as a polymyxin/hydrocortisone ointment. (Malacet, Dermojet® and Oticotic solution, Vedco) Aluminum acetate (Burow’s solution) has also been shown effective for many ear pathogens and as effective as a polymyxin/hydrocortisone ear drop or gentamicin in a group of acute otitis externa cases in humans that were often associated with swimming and 34% had Pseudomonas pyocyanea infections (Lambert 1981; Clayton, Osborne et al. 1990; Thorp, Kruger et al. 1998). In one of these studies stinging from the aluminum acetate drops resulted in their being discontinued in 5% of the cases treated, however another study had no reports of reactions so the formula used may also contribute to reactions. Burrows solution may take 20 minutes of contact to kill organisms (Kashiwamura, Chida et al. 2004). The aluminum can bind and inactivate fluoroquinolones so this type of product should be avoided if concurrent therapy with a topical containing fluoroquinolones is contemplated. A veterinary product of this type is Bur-Otic-HC Ear treatment (Virbac) and as a sole therapy should be used three times a day or more. Tris EDTA increases the permeability of bacterial cell membranes by binding Ca and Mg ions. This activity is mainly apparent in gram negative bacteria including Pseudomonas sp. It is used as a rinse prior to antibiotic application or even mixed with antibiotics to make a combination topical therapy. This combination allows more of the antibiotic to penetrate intra-cellular, even in some resistant strains making them now susceptible. They are synergistic with multiple antibiotics not just aminoglycosides as was originally thought. Tris EDTA was shown to have a sparing effect on the MIC of enrofloxacin against ciprofloxacin resistant Pseudomonas as well as resolve clinical cases resistant to cephalexin or enrofloxacin (Farca, Piromalii et al. 1997; Gbadamosi and Gottelf 2003). It was also shown effective in vivo in a small number of cases when combined with a low level (0.15%) of chlorhexidine digluconate (Ghibaudo, Cornegliani et al.
2004). Recently a product with tris edta and chlorhexidine 0.15% (Dermapet) has become available. Amino acid complexed zinc gluconate (Maxi/Guard® Zn 4.5 Otic™, Addison Biological Laboratory, Inc.) was shown an effective disinfectant against *Malassezia* in canine otitis especially when combined with boric acid and not acetic acid (Mendelsohn, Griffin et al. 2005). Silver sulfadiazine 1% was reported to be an effective antimicrobial in experimentally induced cases of *Pseudomonas* otitis externa (Thomas 1990). It was later showed that it is still effective at lower concentrations down to 0.1%. For silver to be effective it is critical that the bacteria must contact the silver molecule therefore delivery in a total clean ear is essential. Silver sulfadiazene cream 1% is available as Silvadene® Cream (King) or generics but they are thick and not easily applied down ears as is but can be diluted 1to 10 resulting in a 0.1% silver sulfadiazine lotion that more readily can be applied to ears.

Topical antibacterial agents are indicated when bacterial infection, whether primary or secondary, is present. Polymyxin and neomycin are considered first line antibiotics while gentamicin and fluoroquinolones are second line. Third line topical antibiotic options to consider are amikacin, tobramycin and ticarcillin. Many topical antibiotics are less effective when used in dirty ears containing exudate and ears should be kept clean. When used as topical products the concentrations achieved in the ear canal are much higher than that reached with systemic therapy. Often “resistant” bacteria may be sensitive to these higher concentrations especially when concentration dependent cidal antibiotics are utilized. Antibiotics may also be more effective when used with a synergistic agent such as tris EDTA. Antifungal agents are required in any case complicated or caused by the yeasts, *Malassezia* or Candida or dermatophytes. Amino acid complexed zinc gluconate and boric acid was shown effective in treating clinical cases of yeast complicated otitis externa. In vitro or in vivo testing has shown nystatin, miconazole, clotrimazole, enilconazole, ketoconazole, posaconazole, tea tree oil, to be effective against *Malassezia* (Schmidt 1997; Weseler, Geiss et al. 2002; Bourdeau, Marchand et al. 2004).

Systemic antibiotics are used whenever otitis media, moderate or marked proliferative changes are present or when appropriate topical therapy and cleansing were not effective. Initial antibiotic selection is usually made empirically based on cytological findings. When cocci predominate then cephalexin or clavulanic acid/amoxicillin is often prescribed. Methicillin resistant *Staphylococcus intermedius* have been identified in otitis media cases(Cole, Kwochka et al. 2004). Methicillin resistance was performed with the disk diffusion test (DD) for oxacillin and confirmed with the oxacillin screen agar test (OSA). Seven of twenty one were resistant to methicillin. On the OSA screen five of those were susceptible and two strains were still resistant. The methicillin-resistant S. intermedius were susceptible to chloramphenicol, polymyxin B and trimethoprim-sulfadiazine. In mixed infections with cocci present or in cases of cocci not responsive to cephalexin or clavulanic acid/amoxicillin then Potentiated sulfonamides are often prescribed. Fluoroquinolones are usually prescribed when rod shaped bacteria predominate on cytology. The most common fluoroquinolones utilized in the United States include: enrofloxacin (Baytril, Bayer) at 5 mg/kg up to 20 mg/kg q24h, marbofloxacin (Zeniquin, Pfizer) at 2.75-5.5 mg/kg q24hr, orbifloxacin (Orbax, Schering) and ciprofloxacin 5 -10mg/kg q24hr. In cats the maximum dose of enrofloxacin is 5mg/kg once daily as retinal disease and possibly blindness may occur with doses of 20 mg/kg daily, within 21 days of therapy(Wiebe and Hamilton 2002). Marbofloxacin has not been reported to cause this in cats even dosed at twice the high-recommended range. Controlled comparisons of the fluoroquinolones for otitis have generally shown that marbofloxacin is more effective than all the fluoroquinolones except for ciprofloxacin (Martin Barrasa, Lupiola Gomez et al. 2000; DeBoer, Verbrugge et al. 2005; Wildermuth, Griffin et al. 2007). In addition when sensitivity testing the DD testing is acceptable but will identify some strains resistant that based on minimum inhibitory concentration testing are actually susceptible (Colombini, Merchant et al. 2000). This is generally the case with most the aminoglycoside antibiotics as well (DeBoer, Verbrugge et al. 2005). If fluoroquinolones are not effective then sensitivity testing is recommended. If resistance is seen to all oral antibiotics or if sensitivity testing is declined or there are proliferative changes then a fluoroquinolone given with cephalexin at 22 mg/kg q12h may be effective. Whether this reflects a synergistic antibiotic effect or the effect on the concurrent presence of *Staphylococcus* in the deeper tissue is not known. In some cases injectable aminoglycosides are required to eliminate some *Pseudomonas* infections. Gentocin and amikacin are only used when a culture indicates their requirement. These can now be given once daily subcutaneously which has made their use much more tolerable by clients and dogs. Gentocin 6-8mg/kg once daily is less expensive and causes less subcutaneous abscesses than amikacin at 15-20mg/kg. In rare cases Ticarcillin at 15-25 mg/kg q 8 hr IV has been needed.

Systemic treatment for *Malassezia* otitis is most commonly oral ketoconazole (Nizoral, Janssen) 5-10 mg/kg q24h though fluconazole or itraconazole (Sporanox, Janssen) 5 mg/kg q24h. Both ketoconazole and itraconazole have been also used effectively when treated daily for 2-6 days then switched to q48h therapy. One study evaluated itraconazole at 5 mg/kg q24h for two days each week for three weeks and showed this as effective clinically for *Malassezia* otitis as daily for 21 days (Pinchbeck, Hillier et al. 2002).

When therapy is needed for *Otodectes* Selamectin (Revolution or Stronghold, Pfizer) is an approved systemic therapy and preventative treatment (Blot, Kodjo et al. 2003). It is as or more effective than ivermectin, which it has replaced, because of its long duration of one month protection with one treatment. This form of therapy treats the whole pet and will eliminate a carrier state and prevent another infection for one month even in an environment with infected animals.

Systemic glucocorticoid therapy is indicated in markedly inflamed edematous otitis and when chronic pathologic changes cause marked stenosis of the canal lumen. Some cases of allergic otitis may be treated with systemic glucocorticoids allowing for the initial topical therapy to be a low potency glucocorticoid product. Localized atopic otitis will usually respond to topical therapy which should be the ini-
tial treatment. Injectable dexamethasone is useful if only 2-3 days action is required. In more severely inflamed ears, especially when combined with other systemic symptoms, anti-inflammatory dosages of prednisone or prednisolone (1 mg/kg/d) can be used initially and then tapering to the minimum alternate day dosage that controls the symptoms. Triamcinolone acetonide (0.1 mg/kg and tapered as for prednisone) has been superior to prednisone for the treatment of proliferative otitis and otitis externa in cats. In my experience there are also some dogs with proliferative otitis that finally respond when glucocorticoid therapy is changed from prednisone or methylprednisolone to triamcinolone.

Bibliografia


