Selection of appropriate antibiotic and administration route for recurrent canine otitis externa

1480 words

Introduction

Systemic antibiotic therapy is being considered for a 6 year old Cocker spaniel with recurrent otitis externa that has no known allergies or seborrhea. At examination 3 days ago, the left ear was red, malodorous and painful. Cytology revealed rod-shaped bacteria and neutrophils. A sample of ceruminous exudate was submitted for bacterial culture and sensitivity testing and the following was reported: *Pseudomonas aeruginosa* sensitive to ticarcillin and tobramycin, intermediate sensitivity to gentamicin and polymyxin B and resistant to enrofloxacin and marbofloxacin.

Problem list

- Recurrent canine otitis externa
- Multidrug (fluroquinolone) resistant *Pseudomonas aeruginosa*
- Topical versus systemic antibiotic treatment for otitis externa
- Sensitivity testing suggests antibiotics not approved for veterinary use – prescribing 'cascade'
- Treatment failure

Recurrent canine otitis externa

Otitis externa is defined as inflammation of the external ear. Primary causes that directly induce otitis externa include parasites (e.g. *Otodectes cynotis*), hypersensitivity (e.g. atopic dermatitis, food allergy), foreign bodies, disorders of keratin (e.g. seborrhea, hypothyroidism) and immune-mediated disease. The physical characteristics of the ear and ear canal, behavior of dog or owner (e.g. swimming, excessive ear cleaning), immunosuppression, a warm, humid environment, treatment errors and obstruction of the ear canal (e.g. neoplasia) predisposes dogs to developing otitis externa. Secondary and perpetuating causes, such as bacteria and yeasts, otitis media and progressive pathologic change, prevent the resolution of this condition. Classical clinical signs of inflammation (redness, heat, pain and swelling) which can lead to loss

of normal function (deafness) develop following overgrowth of bacteria (usually *Staphylococcus pseudintermedius*) and yeasts (*Malassezia pachydermatis*). Treatment of otitis externa aims to identify and treat the underlying cause, predisposing and perpetuating factors as well as pathogens that may be present.

Multidrug (fluoroquinolone) resistant *Pseudomonas aeruginosa*

Resistance to fluoroquinolones is chromosome mediated and is usually due to amino acid substitutions in DNA gyrase (*gyrA* or *gyrB*) or topoisomerase IV (*parC* or *ParE*) at a site known as the quinolone resistance determining region (QRDR) (reviewed by Bolon 2009). In addition, changes in regulatory factors controlling bacterial permeability such as efflux pumps or alterations in porin channels reduces fluoroquinolone concentrations within bacterial cells. Transferable fluoroquinolone resistance due to plasmids, such as qnr-type determinants, which produce proteins that protect DNA gyrase and topoisomerase IV from fluoroquinolone inhibition, has been identified particularly in Enterobacteriaceae.

The Veterinary Antimicrobial Susceptibility Testing Subcommittee of the Clinical and Laboratory Standards Institute (CLSI) has determined breakpoints for pathogens found commonly in the canine (and feline) for antimicrobial disk and dilution susceptibility tests has established breakpoints for *Pseudomonas aeruginosa* for veterinary approved fluoroquinolones suggest that the organism is resistant at concentrations greater than or equal to 4 μg/mL for enrofloxacin and marbofloxacin and greater than or equal to 8 μg/mL for orbifloxacin (Shryock & Altier 2001). Breakpoints are established based on achievable antibiotic concentrations following systemic administration of antimicrobial agents (Turnidge & Paterson 2007). However following topical administration of approved ototopical preparations containing a fluoroquinolone (enrofloxacin (US only), marbofloxacin and orbifloxacin), the antibiotic concentrations greatly exceed (by around 20–fold or more) these breakpoint values. This would suggest that despite an *in vitro* susceptibility test that would suggest resistance, the organism may in fact be sensitive *in vivo*.

Topical versus systemic antibiotic treatment for otitis externa

Topical therapy delivers treatment at the site of infection and is appropriate for the majority of cases of otitis externa. Many agents used for topical therapy remain at the site of infection (external ear canal) and therefore the risk of systemic side effects is lower than following systemic treatment. All veterinary

approved medication for topical treatment of otitis externa is formulated as polypharmaceuticals, usually containing an antibiotic, antifungal and glucocorticoid. Although inflammation is a feature of all cases of otitis externa, both bacteria and yeast may not be present in all cases. Systemic therapy is required in severe cases of otitis externa and in most cases of otitis media. Severe otitis externa and most cases with otitis media are usually treated systemically, often in addition to topical therapy. In addition, systemic therapy may be used in mild cases of otitis externa where the owner is unable to administer the topical treatment regularly. Most dog owners are able to easily administer oral medication to their dog. Topical treatment is generally effective if administered appropriately and is often less expensive than systemic treatment. Topical treatment should be appropriate in this case.

Sensitivity testing suggests antibiotics not approved for veterinary use – prescribing 'cascade'

The prescribing cascade provisions are based on the European Community Directive 2001/82/EC (as amended). This provides guidance to veterinarians where there is no veterinary medicinal product approved for a specific indication in a specific animal species. On this basis, for a non-food producing animal, a veterinarian can select a veterinary medicine authorised for use in another animal species or for a different condition in the same species; or, if there is no such product either: a medicine authorised for human use; or (based on a valid import permit in line with national regulations), a medicine authorised for veterinary use in accordance with Directive 2001/82/EC (as amended) in another European Member State. Finally, if there is no such product a medicine prepared extemporaneously, by a veterinary surgeon, a pharmacist or a person holding an appropriate manufacturer's authorisation. In this instance, the isolate was listed as susceptible to two antibiotics not approved for veterinary use. However, intermediate susceptibility to two antibiotics approved for veterinary use was reported here. Either of these two agents would make an appropriate choice in the present case, with one alternative approved product containing a fluoroquinolone available as a fallback option.

Treatment failure

Pseudomonas aeruginosa, a Gram-negative bacterium, is not a commensal and is usually found following inappropriate antibiotic therapy. Inappropriate therapy could be due to an inappropriate choice of agent,

incorrect dosing or inappropriate treatment duration. Therapy should be on the basis of a presumptive diagnosis assisted by cytological examination and, particularly if recurrent or chronic, supported by antibiotic susceptibility testing.

The majority of agents available in ototopical preparations have a broad spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria, as well as yeasts. In addition, the majority of antibiotic components in ototopical polypharmaceutical products contain concentration-dependent antibacterial agents (e.g. an aminoglycoside, a fluoroquinolone, polymyxin B) meaning that the higher the concentration of the antibiotic attained the better the killing effect of the agent.

For systemic therapy pharmacodynamic surrogates suggested for clinical efficacy are a ratio of maximum (plasma) concentration (Cmax) to minimum inhibitory concentration (MIC) of around 8 to 12 and/or an area under the curve (AUC) to MIC of somewhere in the region of 35 to 125 hours, depending on the pathogen and the immune status of the patient. This applies not only to the aminoglycosides (tobramycin and gentamicin) and fluoroquinolones (enrofloxacin and marbofloxacin) but also to polymyxin B (Bratu *et al.*, 2005). This makes many of these agents suitable for once daily administration, although not all of those approved for veterinary use are licensed for this. In contrast, ticarcillin is a time-dependent agent and would require concentrations to be maintained at a multiple of MIC for a large part of the inter-dosing interval.

Compliance with treatment is of major importance particularly in the resolution of complex infections. The veterinarian should ensure that the owner is able to comply with treatment including being able to administer the treatment at the correct dosage and frequency for the full treatment course.
If there is some difficulty administering twice daily medication then a product labeled for once daily administration should be selected. If the owner is unable to administer a product into the ear canal as directed then systemic therapy should be considered.

In the treatment of complex infections, such as otitis externa where there are predisposing and perpetuating factors, treatment should be continued for a sufficient period. In less complex cases 5-7 days of treatment may be sufficient but further treatment may be necessary. This means that follow-up examinations will likely be required, particularly in chronic and/or recurrent cases, to assess whether there is sufficient resolution or not.

Conclusion

Topical treatment should be suitable for this case unless the owner is unable to administer this properly. Analysis of the susceptibility test results would suggest that a product containing polymyxin B or gentamicin may be appropriate with the additional option of marbofloxacin. The dog should ideally be re-examined after a further 5-7 days of treatment.

References

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