Antibiotic use in prostatic disease in dogs

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Abstract

Knowledge of pharmacokinetics of currently available antibiotics permits veterinarians to choose antibiotic therapy based on microbial culture and sensitivity results and ability of various classes of antibiotics to readily distribute through prostatic tissue. This may replace other diagnostic tests used to support antibiotic choice, such as measurement of pH of ejaculated prostatic fluid.

Keywords: Prostate, prostatitis, fluroquinolone

Introduction

The prostate is the only accessory sex gland of dogs. It is a retroperitoneal organ, encircling the neck of the urinary bladder. It is bilobed with a palpable median raphe. In smaller breed and younger dogs, it is palpable per rectum. It may be difficult to palpate per rectum in large or giant breed dogs of any age, and in dogs with age-related increase in prostate size and subsequent cranial positioning of the prostate and urinary bladder.

The prostatic capsule is thick and contains smooth muscle fibers, some as an extension of muscle fibers from the wall of the urinary bladder. Some believe there is no such thing as a true prostatic capsule; one study evaluating prostate histology after prostatectomy in men with prostatic carcinoma instead defined a fibromuscular band of varying thickness that was an inseparable continuation of the prostate stroma.[1] The prostatic capsule may be more of a functional than a histologic entity.

The canine prostate is made up of lobules of secretory tissue separated radially by bands of connective tissue. These lobules are larger and contain more secretory tissue in the dorsal and lateral areas of the prostate than in the ventral portion.[2] There is little smooth muscle and less stromal tissue in the canine prostate than in the human prostate. The human prostate also can be separated into three distinct histologic zones (peripheral, transitional, and central); these zones are not evident in dogs.[3]

The primary blood suppy arises via the internal pudental artery as the paired prostatic arteries. The right and left lobes of the prostate are vascularized independently, with the prostatic artery on each side separating into cranial, middle, and caudal arteries. In general, vascularity is poor on the ventral prostate surface compared to the rest of the gland.[4]

Clinical prostatitis

In men, prostate infection or inflammation is classified as acute infectious prostatitis, chronic infectious prostatitis, non-infectious chronic pelvic pain syndrome, or asymptomatic prostate inflammation.[5,6] In dogs, acute and chronic prostatitis are recognized disease entities, with prostatic abscessation generally considered a companion to either. Chronic prostatitis without abscessation will be the focus of this discussion.

Chronic prostatis occurs in the presence of some other prostate disease. The normal canine prostate is protected from ascending infection by anatomic, functional, and immunologic barriers, including secretion of prostatic fluid and urine flow, urethral peristalsis, formation of a urethral high pressure zone at the area of the prostate, and antibacterial properties of prostatic fluid.[7,8] Likelihood of infection is increased by any process that increases the number of bacteria in the periprostatic urethra or urinary

bladder, or that compromises local or systemic immune response.[9] Specific examples include urolithiasis, urethral neoplasia, urinary tract infection, squamous metaplasia of the prostate due to hyperestrogenism with subsequent decrease in prostate secretion, and concurrent prostate diseases such as benign prostatic hypertrophy (BPH) or neoplasia.[7]

The class of organism most often associated with chronic prostatitis in dogs is the Gram negative Enterobacteriaciae, including *E. coli*, *Klebsiella sp.*, and *Proteus sp.* Other bacterial organisms reported include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Brucella canis*.[10-12] Mycoplasma has been reported as a cause of chronic prostatitis,[11] as has blastomycosis.[13] Bacterial organisms implicated in human prostatitis are the same as those in dogs. A complicating factor in human medicine, which may occur in veterinary medicine, is formation of biofilms, a matrix of bacteria and polysaccharide that permits creation of antibiotic-resistant microcolonies within tissue.[14]

Clinical signs are mild, with disease often inapparent. Reported clinical presentations include infertility, poor semen quality, and signs of associated prostate disease such as dripping of bloody fluid from the penis in dogs with concurrent BPH.[12]

Diagnosis is via rectal palpation, imaging, and collection of samples of prostatic tissue or fluid for cytology or culture. Rectal palpation is not an accurate diagnostic test; in one study of 500 dogs, rectal palpation permitted correct identification of prostate disease in only 53% of cases.[15] Rectal palpation can be used to judge prostate size and to assess for a pain response, which usually will be absent in dogs with chronic disease. There are no pathognomic changes visible by ultrasound that permit definitive diagnosis by imaging alone.[16] Most often the infected prostate is described as locally to diffusely hyperechoic.[17] Ultrasound may be best used to guide sample collection; ultrasound-

guided fine-needle aspirate has been reported to be 75% accurate in identifying prostatitis.[18,19]

Culture of prostatic fluid or tissue is required for definitive diagnosis of prostatitis. Culture of ejaculated prostatic fluid is sensitive but not specific as it may be contaminated with organisms from the urinary tract.[20] Results from culture of prostatic fluid correlated well with culture of prostatic tissue in only 80% of instances in one study.[21] Similarly, presence of inflammatory cells in ejaculated prostatic fluid is not well correlated with culture results.[21,22] For these reasons, cytology and culture of prostatic tissue is preferred when possible. The only reported side-effect of fine-needle aspirate of the prostate is transient hematuria.[23]

Treatment involves management of concurrent prostatic or urinary tract disease and antibiotic therapy, as described in detail below. It has been well demonstrated that castration hastens resolution of chronic prostatitis in dogs without prostatic neoplasia as an underlying cause of disease.[11,24] Medical treatment of underlying BPH with finasteride may hasten resolution of disease; the author is unaware of studies evaluating effect of finasteride therapy as a component of treatment for prostatitis in dogs.

Antibiotic pharmacokinetics relative to the prostate

Antibiotics may be characterized by their absorption, distribution, metabolism, and excretion. Factors that affect these processes include lipid solubility, molecular weight, and ionization of the drug molecule, and degree to which the drug is bound to protein in circulation. For antibiotics to penetrate tissue, they must be able to pass through the lipid-rich cell membrane, either by active transfer or diffusion. Since most antibiotics move into cells passively, lipid solubility and size of the molecule are crucial

determinants of ability to penetrate tissue. Environmental pH alters ionization of the cell, which also affect permeability as ionized drug cannot pass through the lipid bilayer. Finally, drug that is bound to protein in serum is unavailable compared to drug that is dissolved and can freely cross cell membranes.[25,26]

Ionization and trapping of drugs due to altered pH has long been upheld as a component of the decision regarding which antibiotic to choose for treatment of chronic prostatitis. The premise is that because charged (ionized) molecules cannot cross the cell membrane and because there may be a pH gradient from serum into prostatic tissue as disease develops within the prostate, uncharged molecules will equilibrate across that membrane but charged molecules will get trapped on one side or the other. If you could trap molecules within the tissue, you'd get a higher concentration of drug on that side (uncharged plus charged portions of the total drug present).[26] Knowledge of the pKa, or ionization constant, would permit one to choose an appropriate antibiotic based on pH of prostatic fluid. The value of this premise is decreased in small animal practice as it has been demonstrated that pH of canine prostatic fluid does not significantly change in the presence of prostate disease,[21] and because of the availability of antibiotics that can ionize at either acicid or alkaline pH.

Fluoroquinolones

Fluoroquinolones are the preferred class of antibiotics for treatment of chronic infectious prostatitis in humans. The fluoroquinolones are bactericidal via inhibition of DNA gyrase, which is necessary for DNA replication and repair.[25] They are well distributed throughout the body because they are lipid soluble and are amphoteric, with both acidic and alkaline ionization constants.[27-29] Fluoroquinolones also move well into

biofilms, lessening chance of persistent or recurrent infection.[27] Products available for oral use in dogs include enrofloxacin (Baytril®; Bayer Animal Health, Shawnee Mission, KS, USA), ciprofloxacin (Cipro®; Schering-Plough, Kenilworth, NJ, USA), marbofloxacin (Zeniquin®; Pfizer Animal Health, New York, NY, USA), orbifloxacin (Orbax®; Intervet/Schering-Plough Animal Health; Summit, NJ, USA), and difloxacin (Dicural®; Fort Dodge Animal Health, Ft. Dodge, IA, USA). Of these compounds, enrofloxacin shows superior movement into canine prostatic tissue, followed by ciprofloxacin and marbofloxacin.[28,30-32]

Macrolides

The macrolide antibiotics are bactericidal or bacteriostatic, depending on bacterial species.[25] Erythromycin is lipid-soluble but is quickly broken down after oral administration and is highly protein bound.[27] Azithromycin concentrates in phagocytes and so is carried into tissue, from which it is slowly released, permitting less frequent dosing.[27,33-35] It has been demonstrated to penetrate the prostate well in humans.[27] There are no veterinary formulations of azithromycin available as of this writing.

Chloramphenicol

Chloramphenicol is bactericidal or bacteriostatic, depending on bacterial species.[25] It is very lipid-soluble and not highly protein bound.[27] Because tissue concentrations generally are well below those in serum, high doses must be used, raising concerns about toxic effects, including myelosuppression, with long-term use.[7]

Trimethoprim-Sulfas

Trimethoprim-sulfa combinations are bacteriostatic as they inhibit DNA replication.[25] These drugs are well absorbed orally and penetrate prostate tissue well.[27]

Concerns of long-term use include keratoconjunctivitis sicca, anemia, and acute neutrophilic hepatitis.[27] The approved veterinary product for dogs is trimethoprim-sulfadiazine (Tribrissen®; Intervet/Schering-Plough).

Other antibiotics

Penicillins and cephalosporins are poorly lipid-soluble and do not penetrate the chronically infected prostate.[27] Aminoglycosides (amikacin, gentamycin) show variability tissue penetration and potential toxicity with long-term use.[27,36] Doxycycline penetrates prostate tissue better than tetracycline but is not commonly used.[27] Metronidazole (Flagyl®; Pfizer, Inc, New York, NY, USA) may be useful if anaerobic infection is a component of disease; it is a lipid-soluble antibiotics that is well absorbed orally and is not highly protein bound.[27] Neurologic signs and gastrointestinal signs may be seen as side-effects.[27]

Conclusion

The primary factor governing antibiotic choice must be the result of culture and sensititivity testing, preferably of prostatic tissue. The chosen antibiotic should be administered for 4 to 6 weeks, with rechecks of prostatic fluid or tissue culture at 7 days, one month and 6 months after completion of therapy.[29,37] Antibiotic resistance may be a growing concern with wide use of fluoroquinolone antibiotics;[38] for this reason an effort should be made to decrease risk of recurrence. Concurrent disease of the urinary tract or prostate must be addressed, including a recommendation for castration in dogs with BPH and recurrent or persistent prostatitis.

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