

## Editorial

# The Penetration of Antibiotics into the Prostate in Chronic Bacterial Prostatitis

Chronic bacterial prostatitis usually presents as a relapsing urinary tract infection (1). The treatment of the underlying prostatic infection continues to be a vexing problem. Long-term cure rates are, at best, only 30–40%. The poor outcome has been attributed, in large part, to the meagre penetration of antibiotics into the prostatic secretions in which the infection occurs (1). In common with a few other “privileged sites” in the body, such as the central nervous system and retina, the prostate gland has a nonporous capillary bed. In order to traverse the capillary endothelium, an antibiotic must pass through the endothelial cell membranes rather than the pores which are found in capillary beds elsewhere in the body. To reach the prostatic secretions, the drug must traverse the additional lipid barrier of the prostatic epithelium. Therefore, drugs which are poorly lipid-soluble, such as penicillins, cephalosporins and aminoglycosides, traverse the capillary wall very slowly. Although it may be argued that the endothelial cell barrier must be disrupted by the inflammatory process, apparently the barrier is well maintained in all but the most acute infections. Only a few commonly used antimicrobial agents are highly lipid-soluble: these include chloramphenicol, rifampin, metronidazole, trimethoprim and certain tetracyclines such as minocycline and doxycycline. Although the antibacterial spectrum of several of these agents, including chloramphenicol, trimethoprim and the tetracyclines, encompasses the gram-negative enteric bacilli which cause the majority of chronic prostatic infections, cure rates of chronic prostatitis with these agents are still low (1). Thus, the problem is presumably more complex than simply finding a lipid-soluble drug with a useful antibacterial spectrum.

Studies of drug levels in human prostatic secretions are exceedingly difficult to carry out. Ejaculate is readily contaminated by small amounts of urine which may contain high levels of drug. Furthermore, it contains secretions of non-prostatic glands. Biopsies, aside from posing obvious logistical problems, are tainted by blood which contains the antibiotic. Although markers such as urea may be sought to detect urinary contamination (2), and fructose or prostaglandins E<sub>1</sub> and F<sub>1 $\alpha$</sub>  (3) to measure the contribution from seminal vesicle fluid, the methodological problems are significant. As a result, the most informative studies have been carried out in animal models.

Three factors are believed to be important in the pharmacokinetic behavior of drugs in the prostate: (a) serum protein binding, (b) lipid solubility, and (c) pH partition (ion trapping). We will review the role of each of these.

Drug binding is the easiest of the three factors to deal with. Presumably, as is true elsewhere in the body, it is the concentration of free drug in the plasma which determines the level of free drug in prostatic secretions (4). The most important molecule in terms of binding of antibiotics is albumin. The concentration of albumin in human prostatic secretions is not known. In one study, doxycycline, which is about 80–90% bound in human plasma, produced somewhat larger zones of inhibition in an agar-diffusion bioassay when dissolved in seminal fluid than when dissolved in plasma, implying somewhat lesser drug binding in the former (5); however, the difference was only 10–18%, so that the differential binding effect may not have been great. Most investigators have ignored this issue completely and used various buffers as standards for prostatic secretions (4–8). It would be helpful to have some data on the binding of drugs by human prostatic secretions in patients with normal and diseased prostates.

Lipid solubility clearly influences the *rate* at which drug enters the prostatic secretions (4, 9). However, if there is no loss of drug within the secretions, lipid solubility should not influence the levels ultimately achieved at equilibrium. Whether a drug is lipid soluble or not, at equilibrium the concentrations of free drug in prostatic secretions should be equal to the levels of free drug in the plasma. However, if the drug is unstable in prostatic secretions, then the levels at equilibrium will be lower than those in the plasma; the differences will be greatest for poorly lipid-soluble drugs. To our knowledge, there is no information on the stability of drugs in prostatic secretions, either in terms of spontaneous breakdown or degradation by bacterial enzymes.

The third factor, that of pH partition or ion trapping by prostatic secretions, has been the most fully investigated. It was brought to the fore when studies in dogs showed that the pH of canine prostatic secretions was only 6.4 (10, 11). It was recognized that drugs such as penicillins and cephalosporins, which are generally weak acids, are less highly ionized in the relatively acidic prostatic secretions than in the plasma. Unionized molecules, being less polar

and more lipid soluble, pass more readily across the lipid barriers than do ionized molecules. Therefore, at equilibrium, the total levels (ionized and unionized species) of weak acids will be lower in prostatic secretions than in the plasma. In contrast, weak bases such as oleandomycin, erythromycin, and the aminoglycosides, which are largely dissociated at the acidic pH of canine prostatic secretions, are "trapped" in these secretions at concentrations exceeding those in plasma. Careful studies in dogs showed that pH partition does occur and that the prerequisites of good penetration into the prostate are a combination of basicity and lipid solubility (12). Presumably, lipid solubility was important in that instance because they were relatively short-term studies.

In 1979, Fair and colleagues (13) found that the pH of prostatic secretions in humans is very different from that in dogs. They reported that normal human prostatic secretions had a mean pH of 7.28 (standard error 0.04) and those from men with documented bacterial prostatitis were *alkaline* with a mean pH of 8.32 (standard error 0.07). Despite considerable interpatient variation in pH values, in no patient with prostatitis was the pH of prostatic secretions less than 7.0. In an earlier study using cruder methods, Blacklock and Beavis had shown fairly similar, though less striking data (14). If, indeed, the pH of prostatic secretions is alkaline in patients with chronic prostatitis, this would militate against the accumulation of weak bases but in favor of trapping weak acids such as penicillins, cephalosporins, sulfonamides and rifampin.

The finding of an alkaline pH in prostatic secretions from patients with chronic prostatitis has implications not only for drug penetration but for drug activity within the prostate (8, 14). The antibacterial effect of tetracyclines, methicillin, cloxacillin and nitrofurantoin is reduced in an alkaline medium. By contrast, the activity of various aminoglycosides and of erythromycin is enhanced at alkaline pH, the very conditions which discourage accumulation of these drugs (15). Indeed, it may be that it is the unionized moiety which is the antibacterially active species for many agents, as has been suggested for erythromycin (15), and that the conditions of pH under which the ionized molecules accumulate are inhibitory to the antibacterial action of the drug. This would be unfortunate for the treatment of bacterial prostatitis.

Of course, factors other than drug penetration may play a role in relapse after treatment (1). For example, organisms within prostatic calculi may be difficult to eradicate, and bacteria which multiply slowly may be poorly susceptible to  $\beta$ -lactam drugs. This emphasizes the need for more understanding of the disease process in chronic bacterial prostatitis as well as of the pharmacokinetic problems in treatment.

To summarize, the problem of drug penetration into the prostate is still with us. Based on data from two

studies, lessons drawn from the standard canine model may not be applicable to humans. If pH partition is important, it may be that weak acids are more likely than weak bases to be concentrated in the secretions of men with chronic bacterial prostatitis. It is also possible that the ionized species which accumulate at the alkaline pH in these patients will be less active than the same drugs at a more acidic pH. Clearly, these issues need to be studied further. Given the chronicity of the disease and its usual treatment, lipid solubility of the drug may not be crucial unless the agent is destroyed in the prostatic secretions, a possibility which also requires investigation. Thus, elucidation of the determinants of the pharmacokinetic behavior of drugs in prostatic secretions remains as frustrating as the clinical outcome of treatment.

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