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Penetration of Antimicrobial Agents into the Prostate

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Abstract
In the present review article, the penetration of antimicrobial agents into prostatic fluid and tissue was examined. Three major factors determining the diffusion and concentration of antimicrobial agents in prostatic fluid and tissue are the lipid solubility, dissociation constant (pKa) and protein binding. The normal pH of human prostatic fluid is 6.5–6.7, and it increases in chronic prostatitis, ranging from 7.0 to 8.3. A greater concentration of antimicrobial agents in the prostatic fluid occurs in the presence of a pH gradient across the membrane separating plasma from prostatic fluid. Of the available antimicrobial agents, β-lactam drugs have a low pKa and poor lipid solubility, and thus penetrate poorly into prostatic fluid, expect for some cephalosporins, which achieve greater than or equal to the inhibitory concentration. Good to excellent penetration into prostatic fluid and tissue has been demonstrated with many antimicrobial agents, including tobramycin, netilmicin, tetracyclines, macrolides, quinolones, sulfonamides and nitrofurantoin.

Introduction

The treatment of patients with prostatic infections, particularly chronic prostatitis, is a difficult medical problem. Neither short- nor long-term therapy with most antimicrobial agents, so effective in the treatment of urinary tract infections, is able to cure chronic bacterial prostatitis, and this is so in spite of the fact that the pathogens are highly sensitive to the antimicrobials used and remain so at the end of the treatment [1]. Investigations on diffusion kinetics of a large number of antibacterial agents in fluids from plasma to prostatic fluid in a normal canine experimental model by Winningham et al. [2] revealed that most of these drugs are unable to cross the electrically charged lipid membrane of the prostate epithelium to reach therapeutic levels within the prostatic acini.

Drug penetration into the prostate gland is thought to be governed by the principles determining drug passage across biological lipid-containing membranes in general. In the absence of secretory or active transport mechanisms, the drug penetration is presumably passive, consisting of diffusion and concentration [3]. Drug characteristics that determine simple diffusion and concentration are lipid solubility, degree of ionization, degree of protein binding and the size and shape of the molecule.

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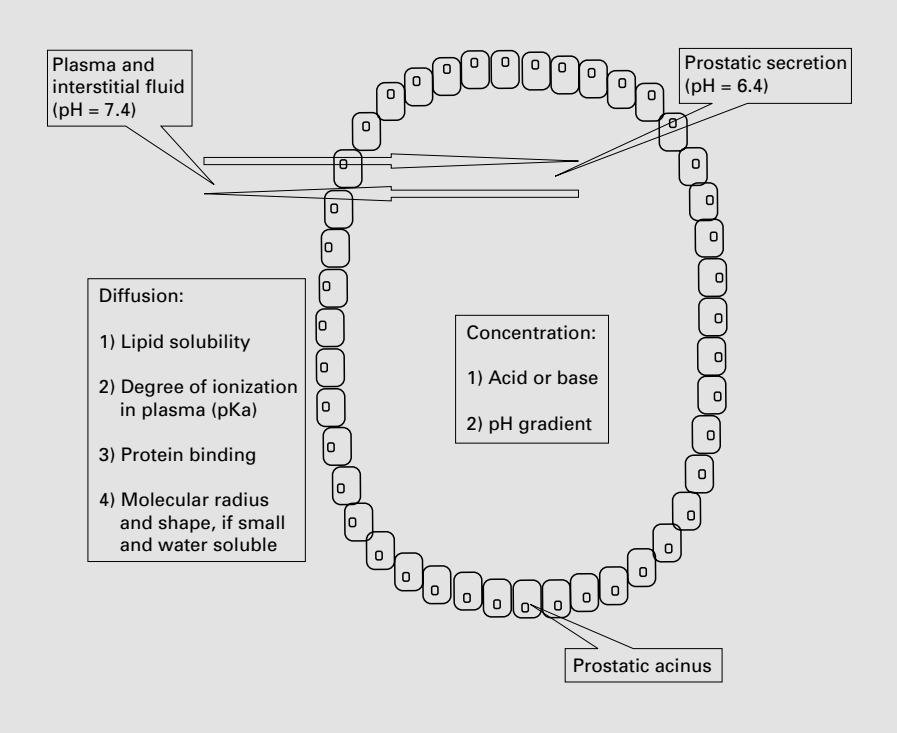

Fig. 1. Factors determining the diffusion and concentration of antimicrobial agents across biologic membranes.

The normal pH of human prostatic fluid is 6.5–6.7 [2]. In chronic prostatitis, the pH increases and ranges from 7.0 to 8.3 [4]. A greater concentration of antimicrobial agents in the prostatic fluid occurs in the presence of a pH gradient across the membrane separating plasma from prostatic fluid [5]. In addition, it is known that only the unionized fraction of antimicrobial agents diffuses readily through cellular membranes [2]. Acid molecules with a dissociation constant (pKa) less than 6.0 are highly ionized at a normal plasma pH, and therefore would be unlikely to diffuse through the prostatic epithelium into the space occupied by prostatic fluid.

The lipid solubility of the molecule also determines the rate of diffusion of drugs across the prostatic epithelium. Only lipid-soluble drugs can cross biological membranes. Since the plasma membrane is a bimolecular lipid leaflet with small pores (4–40 Å), lipid-soluble substances as well as very small water-soluble substances penetrate the membrane by passive diffusion. Therefore, the movement of an antibiotic across the plasma membrane is related to the concentration gradient and the lipid:water partition coefficient. At equilibrium, the concentration of a lipid-soluble drug is the same on both sides of the membrane. If antimicrobial agents with a similar pKa are compared, it is evident that the more lipid-soluble compound demonstrates greater diffusion across biological membranes [3]. There are several other factors beside lipid solubility and ion trapping that can influence drug distribution. Most drugs bind variably to plasma proteins, primarily albumin. Extensive protein binding will tend to lower the amount of free drug available for passive diffusion. Decreased protein binding of antimicrobial agents to plasma or tissue proteins may further improve their penetration into prostatic fluid [2, 4, 5].

In summary, the penetration of antimicrobial agents into prostatic tissue and prostatic secretions depends on absorption, plasma protein binding, lipid solubility, the intercompartment pH gradient and biotransformation. These factors are illustrated in figure 1. Table 1 shows some of the most widely used antibiotic categories with some of their members with respect to their penetration into the prostate.

Penicillins

The natural penicillin, penicillin G, unlike antibiotics with good lipid solubility, penetrates very poorly into the human prostate. This has been shown by findings that levels of penicillin G in canine prostatic fluid are less than

Table 1. Categories of the most widely used antibiotics with some of their members with respect to their penetration into the prostate

Penicillins	*Monobactams*
Amoxicillin/clavulanic acid	Aztreonam
Hetacillin	*Carbapenems*
Piperacillin	Imipenem
Mezlocillin	*Aminoglycosides*
Azlocillin	Gentamicin
Temocillin	Netilmicin
Cephalosporins	*Tetracyclines*
Cephalothin	*Lincosamides*
Cephradine	Clindamycin
Cephalexin	*Macrolides*
Cefaclor	*Quinolones*
Cephazolin	Rosoxacin
Cefamandole	Cinoxacin
Cefonicid	Norfloxacin
Cefotetan	Ciprofloxacin
Cefotiam	Pefloxacin
Cefotaxime	Enoxacin
Ceftriaxone	Ofloxacin
Ceftazidime	Lomefloxacin
Cefmenoxime	Fleroxacin
Cefoperazone	Rufloxacin
Cefpirome	Grepafloxacin
Cefminox	*Trimethoprim-sulfamethoxazole*
Cefpodoxime	*Nitrofurantoin*
Cefuroxime	
Cefazedon	

1% of the simultaneous serum concentrations. Studies in men without prostatitis have typically shown very low levels of penicillin G in prostatic fluid or tissues.

Amoxicillin and Clavulanic Acid Combination

In a study of prostatic tissue and serum concentrations of amoxicillin and clavulanic acid in a fixed combination in 10 patients requiring prostatic surgery, Juricic et al. [6] reported levels of 26.4 and 0.6 μg/ml, respectively, 15–120 min after administration of a single oral dose. Different results were reported by Scaglione et al. [7], who found that the prostatic tissue concentrations of amoxicillin and clavulanic acid in 31 patients undergoing surgery were 0.77 and 0.15 μg/ml, respectively [7].

Hetacillin

Hetacillin is a relatively lipophilic ester that is hydrolyzed in the bowel to ampicillin. The drug penetrates the prostatic membrane fairly well, whereupon it is deesterified to produce ampicillin. In a canine model, the levels of ampicillin in the prostate were twice as high when hetacillin was given than when an equivalent dose of ampicillin was administered [8].

Piperacillin

Piperacillin achieves high and sustained concentrations in prostatic tissue. Tunn and Adam [9] administered 4 g of piperacillin to 21 patients undergoing transurethral resection of the prostate. One hour after injection, piperacillin reached levels of 70.7 μg/g in prostatic tissue compared with 119.1 μg/ml in the serum. Successful treatment was achieved with piperacillin given to patients suffering from chronic bacterial prostatitis in a study by Ponchietti et al. [10].

Mezlocillin

Mezlocillin achieves high concentrations in the prostate. Naber and Adam [11] studied the prophylactic efficacy of mezlocillin in 23 males with benign hypertrophy of the prostate undergoing transurethral resection or suprapubic prostatectomy. Perioperative chemoprophylaxis was started with 5 g of mezlocillin in each patient. Mezlocillin was administered as an intravenous bolus and/or intravenous infusion in various groups of patients. In this study, it was noted that a rapid peak in the prostatic tissue concentration was detected 30 min after mezlocillin administration, but this declined after 60–90 min. The mean tissue concentrations 60 and 90 min after bolus injection of 1 g and after the 1-hour infusion were fairly similar, with values of 76 and 78 mg/kg at 60 min, and 31 and 24 mg/kg at 90 min, respectively. No different clinical effect could therefore be expected using these two modes of administration, since in both groups, the tissue concentrations were sufficiently high to inhibit mezlocillin bacteria. Smith et al. [12] studied the concentrations of mezlocillin in human prostatic tissue in 9 patients undergoing elective suprapubic or transurethral resection of the prostate. Mezlocillin was administered at doses of 2 g intravenously over 20 min 6 h before and at the time of induction of anesthesia, and at the onset of surgery. The average plasma concentration of mezlocillin at the time of tissue sampling was 36.3 μg/ml, and the tissue concentration of mezlocillin at the time of sampling was sufficiently high at a level of 9.4 μg/g. The ratio of the plasma concentration to that of tissue was 0.25. The authors concluded that mezlocillin at appropriate doses achieved a concentration in human prostatic tissue above the inhibitory concentration for common bacterial pathogens.

Azlocillin

In the study referred to above, azlocillin was administered in the same way in 8 patients, and it was found that the average plasma concentration of azlocillin at the time of tissue sampling was 64.9 μg/ml, and the tissue concentration at the time of sampling was 22.9 μg/g [12]. The ratio of the plasma concentration to that of tissue was 0.35. The authors concluded that azlocillin at appropriate doses achieved a concentration in human prostatic tissue above the inhibitory concentration for common bacterial pathogens.

Temocillin

Temocillin is a semisynthetic parenteral penicillin active only against gram-negative bacteria, excluding *Pseudomonas aeruginosa* or *Bacteroides fragilis.* Gould et al. [13] administered temocillin as a single intravenous bolus injection of 1 or 2 g 3–4 h prior to tissue sampling. Peak levels of temocillin in the prostatic tissue were found after 3 h and 45 min at 4.7 mg/kg.

Cephalosporins

Cephalosporins are weak acids with a low pKa, poor lipid solubility and variable protein binding. From a theoretical viewpoint, cephalosporin antibiotics should not achieve high concentrations in prostatic fluid.

Cephalothin

In a study on prostatic secretion of cephalothin, Winningham et al. [2] infused cephalothin intravenously into a dog. A serum level of 63 μg/ml was attained, with a simultaneous prostatic fluid level of only 0.4 μg/ml. This is below the minimal inhibitory concentration for most urinary pathogens.

Cephradine

Cephradine is excreted at satisfactory concentrations in prostatic tissue [14].

Cephalexin

Cephalexin is slightly lipid soluble, although dissociated primarily as an acid (pKa 5.2), is amphoteric and also has a pKa value of 7.3. These features probably are responsible for the low but measurable level of cephalexin found in prostatic tissue [14]. In two studies on human prostatic tissue, the concentration of cephalexin after oral administration was invariably less than 10 μg/ml and was less than 5 μg/ml in the majority of patients [15, 16].

Cefaclor

Cefaclor is an orally administered cephalosporin. Cefaclor achieves levels in human prostatic tissue which are equal to or below the minimum inhibitory concentration of most strains of known facultative bacterial pathogens associated with prostatitis. Smith et al. [17] administered 0.25 and 0.5 g of cefaclor to 10 patients undergoing suprapubic prostatectomy. The average prostatic tissue concentrations were 0.51 and 0.74 μg/g with the 0.25- and 0.5-gram dose, respectively. The ratio of the prostate concentration of cefaclor to that of plasma was approximately 0.7, indicating no evidence of accumulation of the drug in prostatic tissue.

Cephazolin

Cephazolin has been shown to penetrate well into prostatic tissue at high concentrations [16]. Litvak et al. [16] measured the cephazolin concentration in 18 human prostates 45–165 min after intramuscular administration of 500 mg and found that serum concentrations exceeded 15 μg/ml in 17 of 18 patients, but prostatic tissue concentrations were less than 10 μg/ml in 13 of the patients.

Cefamandole

Cefamandole has been shown to penetrate poorly into prostatic tissue and fluid [18].

Cefonicid

Cefonicid has been shown to attain high concentrations in prostatic tissue. Raifer et al. [19] administered 1 g of cefonicid intramuscularly to 11 patients undergoing prostatectomy. One hour after injection, cefonicid reached a level of 13 μg/g in prostatic tissue, and the ratio of the prostate concentration to that of serum was 0.1.

Cefotetan

Cefotetan achieves high and sustained concentrations in prostatic tissue. Concentrations sufficient to inhibit even moderately susceptible bacteria were attained in prostatic tissue. Intravenous bolus doses of 1 g have been shown to produce relatively high peak concentrations of cefotetan of 36 mg/kg in prostatic tissue in patients with prostatic hypertrophy, but not in the prostatic fluid (0.8 μg/ml) of patients with prostatitis [20]. The ratio of the prostatic tissue concentration of cefotetan to that of serum was 0.8.

Cefotiam

In a study by Charton et al. [21], after a single intravenous injection of a 2-gram dose, prostatic tissue taken about 20, 30 and 90 min after dosing had levels of cefotiam of 42, 54 and 16 mg/g, respectively. These findings confirm the satisfactory diffusion of cefotiam within prostatic tissue, although saturation occurs after 30 min.

Cefotaxime

After the usual dose of cefotaxime, therapeutic concentrations occur in the prostate. In the study of Pelz et al. [22], prostatic tissue was obtained 1.5 h after intravenous administration of 2 g of cefotaxime in patients undergoing prostatectomy. The average concentration of cefotaxime was 22.5 μg/g [22].

Ceftriaxone

Ceftriaxone achieves satisfactory concentrations in prostatic tissue. Adam and Naber [23] administered a single intravenous 2-gram dose of ceftriaxone to 46 patients at different points of time, ranging from 30 min to 74 h before the transurethral resection of prostatic adenoma. Thirty minutes after administration, prostatic tissue concentrations of ceftriaxone were between 12.9 and 73.7 μg/g, and after 4 h, they were still between 1.0 and 50.0 μg/g. Even after 48 h, levels of ceftriaxone were between 0.6 and 5.6 μg/g.

Ceftazidime

In the study of Abbas et al. [24], after a 2-gram intravenous dose of ceftazidime, prostatic tissue taken about 1.0, 1.5, 4.0 and 6.9 h after dosing had levels of ceftazidime of 10.1, 6.0, 3.6 and 2.5 μg/g, respectively, and the ratio of the prostatic tissue concentration of ceftazidime to that of serum was 1.4. These concentrations of ceftazidime in the prostatic tissue were greater than the minimum inhibitory concentrations of ceftazidime for gram-negative infections.

Cefmenoxime

Cefmenoxime has been shown to achieve high concentrations in prostatic fluid. In one study including 45 patients undergoing prostatectomy, the average concentration of cefmenoxime in prostatic tissue 40 min after intravenous administration of a 1-gram dose of cefmenoxime was 35 mg/kg [25]. Katoh et al. [26] reported high levels of cefmenoxime in prostatic fluid after an intramuscular dose of 2 g in patients with acute prostatitis.

Cefoperazone

It is well known that cephalosporins do not reach therapeutic concentrations in the prostatic tissue in patients suffering from chronic bacterial prostatitis. Cefoperazone is an exception. Its efficacy and concentrations were studied in 14 patients undergoing transurethral operation due to prostatic hypertrophy [27]. The cefoperazone concentrations in the prostatic tissue were evaluated 60, 90 and in some cases 120 min after the administration of cefoperazone. The average cefoperazone concentration in the prostatic tissue after 60 min was 22.8 mg/kg, and after 90 min, 35.7 mg/kg.

Cefpirome

Cefpirome is a new semisynthetic cephalosporin with an extended antimicrobial spectrum. Cefpirome penetrates the prostate satisfactorily. In one study, the concentration of cefpirome in prostatic tissue was determined in 25 patients undergoing prostatectomy [28]. A single intravenous 1-gram dose of cefpirome was given to the patients before prostatectomy. Prostatic tissue levels 1–2, 4 and 6 h after administration were 10, 9 and 6–8 μg/g, respectively.

Cefminox

The concentration of cefminox sodium, a new cephamycin, in prostatic tissue was determined by Sasagawa [29] in 25 patients with benign prostatic hypertrophy undergoing transurethral prostatectomy. After a 1-gram intravenous dose, prostatic tissue obtained 1 h after dosing had concentrations of cefminox of 5.33 μg/g. The ratio of the prostatic tissue concentration to that of serum was 8.18. There was no correlation between serum and prostatic tissue levels of cefminox.

Cefpodoxime

Cefpodoxime is a new oral cephalosporin with broad-spectrum activity against gram-positive and gram-negative bacteria. Nishimura et al. [30] determined the concentration of cefpodoxime in prostatic fluid obtained by prostatic massage in a patient with chronic prostatitis after 1 week of a dose of 200 mg of cefpodoxime twice daily. About 2–3 h after the final administration, a prostatic fluid concentration of 1.6 mg/l was measured. This is an obvious example of the fact that after 1 week of treatment, prostatic fluid cannot be obtained by prostatic massage without urinary contamination, because the urethra is contaminated with urine voided before, and this urine contains a certain amount of antibiotics. The concentration of cefpodoxime in prostatic tissue between 13 and

18 h after a final administration of 200 mg was found to be 0.38 μg/g in four patients undergoing suprapubic prostatectomy [31].

Cefuroxime

Cefuroxime penetrates into prostatic tissues efficiently and achieves levels well in excess of the minimum inhibitory concentrations for many common pathogens. Becopoulos et al. [32] found that the prostatic tissue concentrations of cefuroxime in 24 patients after administration of 750 mg given either as a single dose or as three intravenous doses daily were 9.87 and 7.62 μg/g, respectively. The ratio of the prostatic tissue concentration to that of serum was 0.69.

Cefazedon

Cefazedon shows excellent penetration into prostatic tissue [33]. In one study, a single intravenous injection of 2 g of cefazedon resulted within 30 min in a mean concentration of 35 μg/g in the prostatic tissue and serum levels of 139 μg/ml. In 5 patients, additional values were estimated after 60 min. At this time, the cefazedon concentrations in the prostatic tissue were 25 μg/g, with simultaneous serum levels of 87 μg/ml.

Monobactams

Madsen et al. [34] showed that the average concentration of aztreonam in human prostate tissue after a 1-gram intramuscular dose was 7.8 μg/g 50–180 min after administration. The average ratio of the prostate concentration of aztreonam to that of serum was 0.25, and it was significantly higher than the minimal inhibitory concentrations for most Enterobacteriaceae implicated in chronic prostatitis [34]. Studies with a dog model have shown that while the concentration of aztreonam in the parenchyma of severely diseased kidneys is reduced compared to that in healthy tissue, it is comparable to the serum level. In prostatic tissue obtained during transurethral resection, the average ratio of the tissue concentration of aztreonam to that of plasma was 0.25 [34]. Atzeotram is excreted in seminal fluid of patients with chronic prostatitis [35].

Carbapenems

Imipenem has been shown to achieve good concentrations in prostatic tissue. Ito et al. [36] and Suzuki et al. [37] administered 0.5 g of imipenem to 4 patients with prostatic hypertrophy. 55–155 min after a single intravenous injection, imipenem reached a level of 5.3 mg/kg in prostatic tissue, compared with 0.2 μg/ml in prostatic fluid 1.5 h after injection in patients with chronic prostatitis or urinary tract infections [36–38].

Aminoglycosides

Aminoglycosides do not penetrate prostatic tissue well, and prostatic tissue levels of these antibiotics are probably inadequate to eradicate gram-negative bacteria. Of the various aminoglycosides, netilmicin has been found to penetrate most effectively into prostatic tissue and fluid.

Gentamicin

Dyderski and Sokolowski [39] studied the prostatic tissue concentrations of gentamicin in 15 patients with periurethral prostatic adenoma without complete anuresis. Gentamicin was administered intramuscularly at doses of 80 mg 1 day before and 60 mg in a single 1-hour infusion immediately before operation. Gentamicin levels in removed adenomas ranged from 1.31 to 3.8 μg/ml, and it was found that the gentamicin concentration in adenomas depended upon their weight (between 18.0 and 45.8 g, respectively). Moreover, the pharmacokinetic parameters of this antibiotic exert a negligible effect on its levels in adenoma.

Netilmicin

Becopoulos et al. [32], in a comparative study including six different antimicrobial agents in 48 patients undergoing prostatectomy, found that netilmicin levels in prostatic tissue were 10.1 and 11.4 μg/g after administration of a single dose of 150 mg and two doses of 150 mg, respectively. The ratio of the prostatic tissue concentrations of netilmicin was 2.53. The authors concluded that netilmicin has a high concentration of the prostate and indicated that this is the agent of choice for prostatic disease, followed by aztreonam, cefuroxime and the ticarcillin-clavulanic acid combination. The ratio of the prostatic tissue concentration to that of serum was 6 times higher for netilmicin compared to amikacin [32].

Tetracyclines

As mentioned above, lipid solubility and degree of ionization are important factors in the passage of various antimicrobial drugs in prostatic fluid. It is well known

that most of the tetracyclines have high lipid solubility [5, 40]. Oxytetracycline could not be detected in prostatic fluid, because the drug has relatively low lipid solubility [5, 40]. Concentrations exceeding those in the serum are obtained in the prostate. Tetracycline is more lipid soluble and can be detected in prostatic fluid in amounts substantially below serum concentrations [40, 41].

Minocycline has been shown to penetrate into prostatic tissue at levels 40–100% of serum concentrations [42, 43]. Hensle et al. [42] measured minocycline concentrations in the prostate in 20 patients undergoing prostatectomy after preoperative intravenous administration of 100 mg. The concentrations of minocycline in the prostate and serum were similar, i.e. 4.6 versus 3.01 μg/g.

Doxycycline concentrations in the prostate have been shown to be 60% of those in serum [44]. Baumueller and Madsen [44] found prostatic concentrations of doxycycline of 40% of those in serum.

Lincosamides

Clindamycin is a lipid-soluble base with pKa values favorable for diffusion into prostatic fluid. Indeed, clindamycin diffuses readily into prostatic fluid, becomes ion trapped on one side of the membrane and reaches levels in prostatic fluid that significantly exceed the levels in plasma [45].

Macrolides

Erythromycin is a lipid-soluble base with pKa values favorable for diffusion into prostatic tissue. Erythromycin penetrates well into prostatic fluid and reaches levels in prostatic fluid that significantly exceed the levels in plasma [46].

Roxithromycin, a new macrolide compound, penetrates well into prostatic tissue. In one study, Botto et al. [47] found that after preoperative administration of roxithromycin in three doses of 150 mg orally at 12-hour intervals, prostatic concentrations of the drug were high. Twelve hours after the last of the three 12-hourly doses of 150 mg of roxithromycin, tissue and serum concentrations were similar.

There are only few data regarding the use of josamycin and clarithromycin in chronic prostatitis cases [48, 49].

Quinolones

Concentrations of several quinolone antibacterials in prostatic tissue or prostatic fluid exceed those in plasma by a factor greater than 1.

Rosoxacin

Rosoxacin is a weak acid which is lipid soluble and moderately protein bound. A rosoxacin infusion sufficient to maintain a plasma level of 11.9 μg/ml resulted in a prostatic secretion level of only 1.4 μg/ml [50]. Prostatic fluid contained 39% as much rosoxacin as did plasma.

Cinoxacin

Cinoxacin is a weak acid, which is relatively insoluble in lipid, but is minimally protein bound. Maigaard et al. [50] found that the concentration of cinoxacin in prostatic secretion was only 3% of the simultaneous plasma levels.

Norfloxacin

Norfloxacin studies have shown that norfloxacin penetrates well into prostatic tissue [51, 52]. The norfloxacin concentrations in prostatic tissue and fluid were similar to those in concurrent sera, and were bactericidal for commonly found pathogens responsible for prostatic infection. In another study by Naber et al. [53], it was found that the concentration of norfloxacin in prostatic fluid was very low. In a study by Shaeffer and Darras [54], norfloxacin showed good results in chronic bacterial prostatitis cases refractory to trimethoprim-sulfamethoxazole and/or carbenicillin [54].

Ciprofloxacin

Penetration of ciprofloxacin into the prostatic tissue is very good, with concentrations consistently above those reached in most other tissues [55–57]. Ciprofloxacin concentrations in prostatic fluid reach particularly high levels 3–10 times higher than the serum levels because ciprofloxacin molecules become trapped inside the prostatic acini. However, these results were not confirmed in two other studies reported later on by Naber et al. [58, 59]. In those two studies regarding ciprofloxacin concentration in prostatic fluid, these investigators found much lower concentrations than those mentioned above [55–57]. Ciprofloxacin may, therefore, prove to be an extremely effective drug for the treatment of prostatitis and urinary tract infections.

Pefloxacin

Pefloxacin achieved equivalent or higher levels in prostatic gland. In one study which included 12 patients undergoing prostatectomy, 400 mg of pefloxacin administered as a single dose produced a peak concentration in prostatic tissue of 1.73 mg/l, while the serum concentration was 2.30 mg/l [60].

Enoxacin

Concentrations of enoxacin have been shown to be higher in the prostate gland than in serum [61, 62]. The levels of enoxacin in serum and prostatic tissue were above the minimal inhibitory concentrations for most urinary pathogens. In general, enoxacin penetrates well into the prostatic fluid [63].

Ofloxacin

Ofloxacin has been shown to penetrate well into prostatic tissue and fluid, and the ratio between the prostatic tissue and serum concentrations was 1.4 ± 0.2 [64, 65]. Naber et al. [65] found that the median concentration of ofloxacin in prostatic fluid was about one third that in plasma.

Lomefloxacin

Lomefloxacin penetrates well into prostatic tissue, and the ratio between the tissue and serum concentrations is >1. In the study of Leroy et al. [66] including 47 patients undergoing prostatectomy, the peak prostatic tissue concentration was 2.07–5.2 mg/l, and the serum concentration was 1.83–10 mg/l. The prostatic tissue concentrations of lomefloxacin were above the minimal inhibitory concentrations for most pathogens responsible for a large percentage of prostatic infections [66].

Fleroxacin

Fleroxacin concentrations in prostatic tissue have been found to be similar to those concomitantly measured in plasma [67]. In 12 healthy volunteers, the concentrations of fleroxacin were measured in plasma and prostatic fluid 2, 4 and 12 h after an oral dose of 400 mg [67]. The mean plasma concentrations of 3 of 4 volunteers at each time point were 4.2, 3.6 and 1.2 mg/l, respectively. The corresponding prostatic fluid ratios were 0.30, 0.27 and 1.26 mg/l, respectively. In the same study, the prostatic fluid and prostatic adenoma tissue concentrations of fleroxacin in 13 elderly patients were similar to those of volunteers. Since this agent is active against almost all bacteria causing complicated urinary tract infections, it should be effective in most cases of bacterial prostatitis [67, 68].

Rufloxacin

In one study including 16 patients undergoing elective transurethral prostate resection, rufloxacin 400 mg was given orally approximately 16 h before surgery, with a further dose of 200 mg approximately 5 h before surgery [69]. The prostatic penetration of rufloxacin appears to be excellent, with prostatic tissue to plasma and prostatic fluid to plasma concentration ratios of 1.9 and 1.5, respectively. The individual rufloxacin concentrations in prostatic tissue and fluid are far above the MFCs for the majority of microorganisms involved in chronic bacterial prostatitis [69].

Grepafloxacin

Suzuki et al. [70] found that in patients (number not indicated) receiving grepafloxacin 200–300 mg/day for 5 days for the treatment of complicated urinary tract infections, the maximum drug concentration in prostatic fluid was 0.03–0.53 mg/l at 1–4 h, achieving a ratio of prostate fluid concentration to that of serum of 0.12–1.71.

In general, the concentrations of the newer quinolones in prostatic fluid and prostatic tissue are relatively high in comparison to corresponding plasma concentrations, in contrast to β-lactam antibiotics. Studies showed that prostatic tissue concentrations exceeded the corresponding tissue concentrations, with some differences between the quinolones. The results are not directly comparable, however, because different techniques of tissue preparation and analysis were used.

Trimethoprim-Sulfamethoxazole

It has been shown both theoretically and to some extent experimentally that only lipid-soluble bases with a high pKa can pass through the prostatic epithelium and become concentrated in the acini. In contrast to sulfamethoxazole, trimethoprim is a lipid-soluble base with a pKa value of 7.3, indicating that more than half of it is unionized and available for diffusion. In agreement with this, trimethoprim at the dose usually recommended has been shown to have a ratio for the noninflamed prostatic fluid concentration to that of plasma of 1.5–2 [71]. At equilibrium state, the ratio of the concentration of trimethoprim in noninflamed prostatic tissue to that in plasma varied from 2.0 to 2.3, while values for sulfamethoxazole varied from 0.3 to 0.5. The trimethoprim to sulfamethoxazole ratio in prostatic tissue is 1:2 to 1:6 [72]. In many studies, trimethoprim concentrations in the human prostate have been found to be 2–3 times higher than that in plasma [73].

Winningham and Stamey [74] and Robb et al. [75] found a plasma concentration of sulfamethoxazole 10 times higher than that of prostatic fluid. The prostate concentration of sulfamethoxazole in one study was high, and the ratio of the plasma concentration to that of the prostate varied from 1.25 to 3.29 [71].

Although the plasma trimethoprim to sulfamethoxazole ratio generally exceeded 1:10, the prostatic tissue ratio was usually <1.3. In one study, the secretion ratio of trimethoprim to sulfamethoxazole was 7:1, while in another, the ratio was 2.5:1 [76, 77]. Although Dabhoiwala et al. [72] believe that sulfamethoxazole achieves sufficient concentrations in prostatic tissue to be synergistic with trimethoprim, it is not clear that this is true for prostatic secretion [74, 75].

Nitrofurantoin

Nitrofurantoin is a lipid-soluble weak acid with a pKa value that is somewhat favorable for diffusion into prostatic fluid [78]. Although low levels of nitrofurantoin were achieved in prostatic fluid in dogs, the administration of standard oral doses of this drug to men results in levels of ≤ 1 μg/ml of blood; such levels guarantee that the levels attained in prostatic fluid will be nontherapeutic.

Conclusions

In conclusion, drug solubility, degree of ionization and degree of protein binding, as well as the size and the shape of the drug molecule, are the main factors involved in the process of drug penetration into the prostate. Antimicrobial drugs presenting a low pKa and a poor lipid solubility penetrate poorly into the prostate tissue. Among a large number of members of the various antibiotic categories used nowadays, good to excellent penetration into the prostate has been demonstrated with a broad spectrum of antimicrobial agents discovered/synthesized recently, e.g. some of the newer quinolones. In general, reported data on prostatic tissue penetration by various antimicrobial drugs, as presented in our bibliography, must always be considered cautiously with a critical view of the methodology used, since controversial results have been reported [79]. The physician has to take into account a number of patient-related factors in order to decide on a specific treatment.

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