Moxalactam Concentrations in Human Prostatic Tissue

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Received 9 February 1983/Accepted 26 April 1983

The concentrations of moxalactam in human prostatic tissue, obtained by enucleation or transurethral resection, were measured in 10 patients after the intramuscular administration of two 500-mg doses. The average concentrations of moxalactam in prostatic tissue in the enucleated and transurethral resection specimens were 4.0 μg/g and 5.2 μg/ml, and the ratios of the moxalactam concentrations in prostate to those in plasma were 0.24 and 0.31, respectively. The concentrations of moxalactam achieved in prostatic tissue after the administration of relatively low doses were greater than the minimum inhibitory concentrations of moxalactam for most common gram-negative pathogens. Concentrations of moxalactam in carefully obtained transurethral resection specimens were similar to those found in the enucleated specimens.

Treatment of chronic bacterial prostatitis is hampered by poor penetration of most antimicrobial agents into prostatic secretions and tissue (13, 19, 23). Therefore, even prolonged therapy during which high concentrations of antibiotics are attained in serum frequently fails to eradicate infection and prevent relapses of urinary tract infections caused by gram-negative bacterial pathogens (8, 11, 12, 16, 17). Since moxalactam is significantly more effective in vitro than most other β-lactams against common urinary pathogens (24, 27), the penetration of this agent into the prostatic tissue of patients undergoing elective suprapubic or transurethral resection of the prostate (TURP) has been studied, with the results recorded in this report.

MATERIALS AND METHODS

 Patients. Five patients undergoing elective suprapubic prostatectomy and five patients undergoing TURP were studied. Informed consent, according to the guidelines of the Committee on Research Involving Human Subjects at the Albany Medical College, was obtained from all patients. The patients had no serious underlying disease. Their average age was 66 years (range, 55 to 82 years); their average weight was 75.5 kg (range, 65 to 86 kg). Urine cultures were negative on the day of surgery. Levels of creatinine in serum were <1.4 mg/100 ml.

 Drug administration. Moxalactam (500 mg) was administered intramuscularly 12 h before and at surgery.

 Surgery and specimen preparation. TURP was performed using a Stern-McCarthy resectoscope, with the patient under spinal anesthesia. The sheath of the resectoscope was introduced through the urethra, the bladder was emptied of urine, and irrigation with 1% glycine was begun. Under direct inspection, a single 1.5- to 2.0-g specimen of prostatic adenoma tissue was excised, washed immediately in normal cold saline, and placed in a sterile container at 0°C.

 Tissue obtained at suprapubic or retropubic enucleation of the prostate was immediately washed and cooled as described above, and random 0.5- to 1.0-g samples were removed from the subcapsular areas after inspection by the surgeon and the pathologist. The capsule was stripped, and the tissue was processed.

 Prostatic tissue obtained by either surgical technique was washed in cold isotonic saline, snap frozen in CO₂-acetone, and stored at −70°C until assayed. Plasma and urine samples were obtained immediately after TURP.

 A moxalactam standard (Eli Lilly & Co., Indianapolis, Ind.) was prepared at a concentration of 1,000 μg/ml in phosphate buffer (pH 6.0) on the day of surgery. Plasma, urine, and standard moxalactam samples were stored at −70°C until assayed.

 In vitro studies. (i) Prostatic homogenates. Prostatic tissue was prepared by dicing frozen tissue and homogenizing it in cold phosphate buffer (pH 6.0) for 30 s in a tissue homogenizer (Tekmar Co., Cincinnati, Ohio). The homogenate was diluted with phosphate buffer to a concentration of 1 g of tissue per 10 ml of buffer. The homogenate was then spun for 30 min at 2,000 rpm, and the supernatant was used in the assay.

 (ii) M oxalactam concentrations. (a) Plasma and urine. Concentrations of moxalactam in plasma and urine were determined by the agar diffusion method, using cut wells. The assay plates were prepared with seed agar antibiotic medium A (BBL Microbiology Systems, Cockeysville, Md.) and inoculated with a 0.25% Escherichia coli ATCC 10536 suspension which was previously grown for 18 to 20 h at 30°C in antibiotic medium 3 (Difco Laboratories, Detroit, Mich).

 (b) Prostatic tissue. Concentrations of moxalactam in prostatic tissue were determined by an agar diffusion method, using Penassay cylinders. The assay plates were prepared with Trypticase soy agar (BBL Micro-
TABLE 1. Moxalactam concentration in human prostatic tissue and plasma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time (h) after moxalactam administration</th>
<th>Moxalactam concn. (µg/g)</th>
<th>Ratio (prostate/plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prostatic tissue</td>
<td>Plasma (µg/ml)</td>
<td></td>
</tr>
<tr>
<td>10a</td>
<td>1.0</td>
<td>4.3</td>
<td>17.2</td>
</tr>
<tr>
<td>2b</td>
<td>1.0</td>
<td>7.3</td>
<td>17.8</td>
</tr>
<tr>
<td>8a</td>
<td>1.25</td>
<td>6.1</td>
<td>20.6</td>
</tr>
<tr>
<td>7b</td>
<td>1.7</td>
<td>6.9</td>
<td>29.2</td>
</tr>
<tr>
<td>9a</td>
<td>1.8</td>
<td>5.2</td>
<td>22.2</td>
</tr>
<tr>
<td>3b</td>
<td>2.0</td>
<td>4.3</td>
<td>20.1</td>
</tr>
<tr>
<td>5b</td>
<td>2.0</td>
<td>3.6</td>
<td>16.2</td>
</tr>
<tr>
<td>6a</td>
<td>2.0</td>
<td>3.6</td>
<td>16.6</td>
</tr>
<tr>
<td>1b</td>
<td>4.5</td>
<td>2.3</td>
<td>8.5</td>
</tr>
<tr>
<td>4b</td>
<td>5.0</td>
<td>2.3</td>
<td>5.1</td>
</tr>
</tbody>
</table>

a Tissue obtained by TURP.
b Tissue obtained by enucleation.

Many antibiotics have been evaluated for penetration into canine prostatic tissue and prostatic secretion and for penetration into human prostatic tissue obtained by TURP (1–7, 9, 10, 14, 15, 18–23, 25, 26, 28). In the canine model, the penetration of β-lactams into prostatic secretion is negligible, and β-lactam concentrations in human prostatic tissue obtained by TURP seem high (1–5, 20, 21). Contamination of the resected prostatic tissue during TURP is the likely reason for these frequently obtained high moxalactam concentrations in tissue (28). The concentrations of only one β-lactam antibiotic, cefaclor, have been studied in prostate tissue obtained by enucleation, and the concentrations are known to be <1.0 µg/g (22).

Concentrations of moxalactam in prostatic tissue were similar in patients undergoing suprapubic prostatectomy or TURP. Although concentrations of moxalactam in plasma were higher in the TURP group of patients, this finding is most likely related to the shorter time between the administration of the drug and the time of the resection of the tissue.

The concentrations of moxalactam in prostatic tissue obtained by enucleation and TURP are markedly higher than the minimum inhibitory concentrations of most gram-negative urinary bacterial pathogens (24). The similarity of concentrations of moxalactam in tissue obtained by either surgical procedure suggests that urine contamination of carefully obtained tissue in TURP does not contribute to the levels obtained in our laboratory. Because of enhanced antibacterial activity, resistance to β-lactamases, and moderately long serum half-life and concentrations of moxalactam in tissue obtained in this study, moxalactam might be a valuable β-lactam cephalosporin in the treatment of bacterial prostatitis caused by susceptible organisms.

ACKNOWLEDGMENTS
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biology Systems) supplemented with 0.1% dextrose and 1.0% sodium acetate. The plating medium was inoculated with 0.1% Providencia spp. 63 which was previously prepared in antibiotic medium 3 and adjusted to 25% transmission at 530 nm with a Bausch & Lomb Spectronic 70 spectrophotometer.

Standard curves were generated by preparing moxalactam standards in phosphate buffer (pH 6.0) for prostatic tissue and urine assays and in homologous plasma for the plasma assay. The concentrations of moxalactam in micrograms per milliliter or micrograms per gram were determined by measuring the size of the zone of inhibition surrounding the Penassay cylinder or the cut well in samples containing known moxalactam standard concentrations and test samples.

To test for possible binding or inactivation of moxalactam by prostatic tissue, resected prostatic tissue from three subjects not receiving antimicrobial agents was incubated with moxalactam in vitro. Recovery of moxalactam by bioassay was 94% (range, 93 to 96%), indicating the availability of unbound drug in the assay system. All moxalactam concentrations in tissue were determined in duplicate.

RESULTS

Table 1 shows the concentrations of moxalactam in plasma and in prostatic tissue as well as the time of tissue sampling relative to the second dose of moxalactam. The concentrations of moxalactam in prostatic tissue obtained by enucleation ranged from 2.3 to 7.3 µg/g, and those in tissue obtained by TURP ranged from 3.6 to 6.9 µg/g. The mean time after the second dose of moxalactam was less and the plasma concentration was higher in the TURP group than in the patients undergoing prostatectomy by enucleation.

The ratios of the moxalactam concentrations in prostate to those in plasma ranged from 0.22 to 0.45. No patient had concentrations of moxalactam in prostatic tissue greater than those in plasma. The concentrations of moxalactam in urine ranged from 158 to 1,230 µg/ml (mean, 586 µg/ml), with no relationship between concentrations in urine and prostate.

DISCUSSION

Many antibiotics have been evaluated for penetration into canine prostatic tissue and prostatic secretion and for penetration into human prostatic tissue obtained by TURP (1–7, 9, 10, 14, 15, 18–23, 25, 26, 28). In the canine model, the penetration of β-lactams into prostatic secretion is negligible, and β-lactam concentrations in human prostatic tissue obtained by TURP seem high (1–5, 20, 21). Contamination of the resected prostatic tissue during TURP is the likely reason for these frequently obtained high moxalactam concentrations in tissue (28). The concentrations of only one β-lactam antibiotic, cefaclor, have been studied in prostate tissue obtained by enucleation, and the concentrations are known to be <1.0 µg/g (22).

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