Intrarenal Concentrations of Ampicillin in Acute Pyelonephritis

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The intracortical, medullary, and papillary distribution of ampicillin was studied in normal and pyelonephritic rats. At 4 days after induction of pyelonephritis, the animals were given a single injection of 100 mg of ampicillin per kg or were treated for 1 week with two daily doses of 100 mg/kg. Major differences in the intrarenal distribution of ampicillin were noted between normal and pyelonephritic animals. At 2 hours after injection, the concentrations of ampicillin in all parts of the infected kidneys were significantly lower (P < 0.05) than in normal kidneys. The area under the curve (micrograms·minute per milliliter) over a 4-h period after single injection was much lower in the medulla (6.3 ± 0.9) and papilla (29.6 ± 4.2) of infected kidneys than in the medulla (11.2 ± 1.6) and papilla (44 ± 10.1) of noninfected kidneys. Whereas the ratio of concentration in tissue to concentration in serum ranged to 11.1 in the papilla of normal animals, this ratio was reduced to 2.4 in the presence of pyelonephritis. The diminution of the concentration gradient was also striking in the urine, where there was a reduction of more than threefold in pyelonephritic animals. One week of therapy resulted in a noticeable reduction of the inflammatory process associated with a return to near-normal intrarenal distribution of ampicillin. In normal rats treated with multiple doses, there were decreases of the antibiotic concentrations in serum and kidneys and in the area under the curve for these tissues.

Ampicillin is a commonly used agent in the treatment of urinary tract infection. The intrarenal distribution of ampicillin in normal rats (4) and in nondiseased human kidneys (15) has been studied, as well as its distribution in end-stage human kidneys (15), but there are no data available on the influence of acute infection on the intrarenal distribution of ampicillin.

The purpose of this study was to compare the cortical, medullary, and papillary distribution of ampicillin after 1 or 14 doses in normal rats and rats with pyelonephritis.

MATERIALS AND METHODS

Female Sprague-Dawley rats weighing between 200 and 240 g were used for all experiments (2, 14). The animals were allowed free access to food and water. They were fed a standard rat diet free of antibiotics. The serum concentrations, intrarenal distribution, and urinary levels of ampicillin were evaluated in normal and infected rats after 1 or 14 injections of 100 mg of drug per kg of body weight.

Shortly before each experimental period, the rats were weighed and anesthetized by intraperitoneal injection of sodium pentobarbital (60 mg/kg). Pyelonephritis was induced by two medullary inoculations of 0.05 ml of an inoculum of 10^6 Escherichia coli (ECY 9 strains furnished by V. Andriole, Yale University) through the upper and lower poles of the left kidneys. On day 4 after inoculation, the left kidneys of the animals were weighed, and infected kidneys were stripped of their capsule, weighed, and slit by longitudinal incision. Cortical, medullary (outer medulla), and papillary (inner medulla-papillary tip) components were separated under a dissecting microscope. The accuracy of the

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analyses were infected controls and physiological assay antibiotic subtilis in injection studies. pathological and assays were in serum, and homogenates of cortex, medulla, and papilla homogenates for renal tissue. Recovery of ampicillin after the addition of known amounts of drug-free homogenates of cortex, medulla, and papilla was 94 ± 6%.

Kidneys from all groups were subjected to histopathological studies. Of 72 rats, 36 received a single injection of the antimicrobial agent, and 36 were treated for 1 week. Of these 36 rats, 18 were noninfected controls and 18 were infected rats.

The volume of distribution of ampicillin in the papilla was estimated by the methodology of Whelton et al. (16). The half-lives, the area under the curve (AUC) and the volume of distribution in the papilla were determined by standard methods (9, 10). Protein binding of ampicillin to rat serum and kidney tissue was determined as previously described (2). Statistical analyses were performed by using the Student t test.

### RESULTS

**Histopathology.** After the rats were treated with ampicillin for 1 week, the left kidneys showed signs of chronic pyelonephritis of moderate severity with focal areas of scarring, and they were in general smaller than the right kidneys, which showed no signs of inflammation.

**Serum.** The concentrations of ampicillin in serum are presented in Table 1. In normal rats, peak concentrations of ampicillin in serum were 60.3 ± 8.5 μg/ml after one injection and 23.1 ± 3.7 μg/ml when 14 doses were given (P < 0.01).

In infected rats, the peak serum levels (Table 1) of ampicillin after one injection were comparable to those in normal rats. The half-life of ampicillin in the serum of pyelonephritic animals after 14 injections was shorter (0.25 ± 0.03 h) than in normal animals (0.46 ± 0.07 h) (P < 0.01).

The AUC in normal rats was higher (P < 0.01) after 1 injection (5.9 ± 0.5 μg·min/ml) than after 14 injections (1.5 ± 0.2 μg·min/ml) (Table 2). The AUC was slightly lower (P < 0.05) in infected rats. After 14 injections, the AUC was slightly higher in infected animals (P < 0.05).

**Kidneys: cortical, medullary, and papillary areas.** In Fig. 1, concentrations of ampicillin in the cortex, medulla, and papilla of normal

### Table 1. Serum concentration, amount, and percent of the dose of ampicillin recovered in urine after 1 or 14 injections in normal and pyelonephritic rats

<table>
<thead>
<tr>
<th>No. of injections</th>
<th>Rat</th>
<th>Serum concn (μg/ml) at time (h)</th>
<th>Ampicillin excreted in urine in 1st 4 h (mg)</th>
<th>% of dose recovered in urine in 1st 4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>60.3 (8.5)*</td>
<td>12.2 (1.1)</td>
<td>67.5</td>
</tr>
<tr>
<td></td>
<td>Pyelonephritic</td>
<td>62.8 (2.9)</td>
<td>5.8 (0.7)</td>
<td>30.6</td>
</tr>
<tr>
<td>14</td>
<td>Normal</td>
<td>23.1 (3.7)</td>
<td>8.3 (0.6)</td>
<td>36.6</td>
</tr>
<tr>
<td></td>
<td>Pyelonephritic</td>
<td>38.4 (3.6)</td>
<td>7.1 (1.1)</td>
<td>33.4</td>
</tr>
</tbody>
</table>

* Figures within parentheses are the standard error of the mean.

### Table 2. AUC of ampicillin in the serum, cortex, medulla, and papilla of normal and pyelonephritic rats after 1 or 14 injections

<table>
<thead>
<tr>
<th>No. of injections</th>
<th>Rat</th>
<th>Serum</th>
<th>Cortex</th>
<th>Medulla</th>
<th>Papilla</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>5.9 (0.5)*</td>
<td>8.0 (0.6)</td>
<td>11.1 (1.6)</td>
<td>43.8 (10.1)</td>
</tr>
<tr>
<td></td>
<td>Pyelonephritic (right)*</td>
<td>4.4 (0.2)</td>
<td>6.0 (0.8)</td>
<td>5.8 (0.9)</td>
<td>28.3 (4.2)</td>
</tr>
<tr>
<td></td>
<td>Pyelonephritic (left)*</td>
<td>1.6 (0.2)</td>
<td>1.6 (1.5)</td>
<td>6.4 (1.3)</td>
<td>17.7 (1.9)</td>
</tr>
<tr>
<td>14</td>
<td>Normal</td>
<td>1.5 (0.2)</td>
<td>2.5 (1.2)</td>
<td>3.2 (1.1)</td>
<td>16.0 (8.9)</td>
</tr>
<tr>
<td></td>
<td>Pyelonephritic (right)</td>
<td>2.4 (0.3)</td>
<td>3.2 (1.2)</td>
<td>2.8 (0.5)</td>
<td>6.0 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Pyelonephritic (left)</td>
<td>2.2 (0.7)</td>
<td>2.8 (0.5)</td>
<td>2.8 (0.5)</td>
<td>6.0 (0.5)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are the standard error of the mean.

* Right kidneys infected by reflux.

* Left kidneys infected by direct inoculation.
and infected kidneys in animals which either received one injection or 1 week of therapy are compared. At 2 h after either single or multiple doses, the concentrations of ampicillin in various sectors of the kidneys of infected animals were significantly lower ($P < 0.05$) than those in normal animals. On the other hand, at 4 h after a single dose, the concentrations of ampicillin were higher within the cortex, medulla, and papilla of infected rats than in normal animals. The levels of drugs in the normal and infected kidneys were always lower in animals which received multiple doses over 1 week than in recipients of a single dose. This diminution was more striking in normal animals than in infected rats ($P < 0.01$).

After one dose, the AUC in the medulla and papilla was lower in infected than in normal animals ($P < 0.05$) (Table 2). No noticeable difference was noted between the AUC in the cortex and medulla of normal and infected animals treated for 7 days.

Figure 2 shows the ratio of tissue to serum concentrations. These ratios were reduced in the pyelonephritic animals. Whereas there was an increase of up to 11.1 in this ratio between the cortex and the papilla of noninfected kidneys, this concentration gradient was reduced to 2.3 in the left kidneys, where infection was more severe.

The volume of distribution of ampicillin in the

![Diagram](http://aac.asm.org/)
was recovered in the urine of normal rats, whereas after 14 injections, only 36.6% could be detected. In infected rats, the recovery of ampicillin after 1 injection (30.6%) was only half that in normal rats, whereas there was no difference between ampicillin recovery rates in infected animals (33.4%) and normal animals (36.6%) after 14 injections.

The ratios of urine concentration to serum concentration (Fig. 2) were almost the same after 1 or 14 injections in normal rats. The ratios in infected rats were decreased by more than threefold.

The average volumes of urine produced over 1 h were 0.13 ± 0.01 and 0.18 ± 0.02 ml in normal rats after 1 and 14 injections, respectively, and 0.25 ± 0.02 and 0.33 ± 0.02 ml in infected rats after 1 and 14 injections, respectively.

The binding of ampicillin to rat serum was 72.7 ± 0.8%. It was 34.2 ± 1.3% in the cortex, 10.3 ± 1.9% in the medulla, and 45.7 ± 4.4% in the papilla.

DISCUSSION
This investigation establishes major differences in the intrarenal distribution of ampicillin in normal and pyelonephritic animals. In non-infected rats, there was a moderate gradient of concentration between serum, cortex, and medulla, with a much larger gradient in the papilla. This observation is in accordance with those of other investigators (4). In contrast, such a gradient was not apparent after administration of ampicillin to humans (15) or dogs (16), but was observed in dogs treated with penicillin G (16). It is not clear whether the lower amount of binding of ampicillin to human serum (20%) than to rat serum (73%) might have played a role in the gradient observed between species.

The decrease in the concentration of ampicillin within the medulla, the reduced intrarenal concentration gradient, and the reduction of the AUC in the medulla, the site of bacterial proliferation in pyelonephritis (13), further support the disturbing role of infection in the intrarenal distribution of this antibiotic. Low levels of ampicillin noted in end-stage human kidneys (15) confirm our present observation. Another group (11) has observed a decrease in the concentrations of tetracycline in the kidneys of rats with pyelonephritis.

The local inflammatory process present in pyelonephritis, the impaired tubular secretion, and the localized vasoconstriction which could be induced by bacterial toxin could be contributory factors to the disturbed intrarenal distribution of ampicillin. The absence of production of beta-lactamase by E. coli used in our experiments suggests that local destruction of the ampicillin by bacterial enzymes is unlikely. Disturbed binding of ampicillin to injured kidney tissue should also be considered.

The impairment in the urinary concentrating ability, as indicated by increased urinary volume and diminished urinary concentration of ampicillin, further supports the observation that the countercurrent multiplier system may be severely affected in pyelonephritis (12).

The two- to threefold increase in volume of distribution of ampicillin in the infected papilla resulted because disrupted tubular cells allowed ampicillin to diffuse in the interstitium of the papilla. It is of interest to note that the small volume of distribution of ampicillin noted in the noninfected papilla is in accordance with previously published data (16).

Our study evidenced a difference in the pharmacokinetics of ampicillin in normal animals after 1 or 14 injections. There may be several explanations for the decrease of both the antibiotic concentrations and the AUC for serum and kidneys after multiple doses, along with the diminished recovery of the drug in the urine. Knudsen et al. (6) also found this decrease for the serum concentration. Among the explanations may be: (i) activation of other routes of excretion; (ii) induction of liver or kidney enzymes metabolizing ampicillin (3) or another ampicillin transformation process (7, 8); (iii) modified tissue binding; and (iv) development of antibody to the antibiotics (1). Poor absorption after multiple doses or local enzymatic destruction at the peritoneal site have also been cited as possible causes for these pharmacokinetic differences, but our previous experiences with other drugs administered intraperitoneally, including gentamicin and netilmicin (2), or trimethoprim and sulfamethoxazole (unpublished data) do not argue in favor of poor peritoneal absorption with multiple intraperitoneal doses. These possibilities are under investigation.

One week of therapy resulted in a noticeable diminution in the inflammatory process, which
was associated with a return to normal values of AUC of ampicillin in the right kidney. On the other hand, persistence of scarring in the left kidney might have been responsible for the severe lowering of the intrarenal gradient observed in our study.

It is hard to speculate on the therapeutic implications of our observation, but one may conclude that the poor penetration of ampicillin into the infected renal parenchyma, especially the medulla, may impair the local activity of this antibiotic and may be an added cause of failure of therapy in pyelonephritis.

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LITERATURE CITED


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