Efficacy of Cinoxacin in Urinary Tract Infections

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Cinoxacin, a new synthetic antibacterial agent with in vitro activity against all species of Enterobacteriaceae, was used in the treatment of urinary tract infections in 20 patients. The dose of cinoxacin was 250 mg orally every 6 h for 10 days. The etiological agents were Escherichia coli in fifteen, Klebsiella-Enterobacter in five, Proteus mirabilis in two, and Providencia in one. The minimal inhibitory concentration for these organisms ranged from 2 to 64 μg/ml. Eleven of the 20 patients had renal involvement by defined criteria, whereas the remaining nine were considered to have bladder bacilluria. The initial strain was eradicated during and immediately after treatment in 19 of 20 cases. At 6 weeks, 65% had sterile urine. Bactericidal urine levels of cinoxacin were obtained in all patients. No significant hematological, renal, hepatic, or gastrointestinal toxicity was noted. Cinoxacin appears to be a safe and useful drug in the treatment of urinary tract infections caused by Enterobacteriaceae.

MATERIALS AND METHODS

Twenty patients from the outpatient clinics of the University of Illinois Hospital (19 female and 1 male, range 19 to 78 years) with a diagnosis of urinary tract infection were treated with cinoxacin. Criteria for inclusion in the study (Table 1) were bacilluria of >10^9 organisms/ml, pathological pyuria with >25,000 leukocytes/ml of unspun urine, and symptoms of frequency, dysuria, and/or flank pain.

Eleven patients (55%) were thought to have renal involvement on the basis of two or more of the following criteria: abnormal pyelogram with calycal blunting, flank pain and/or tenderness, antibody-coated bacteria, or persistent isolation of the same bacterial strain with associated pathological pyuria. The remaining nine patients were considered to have bladder bacilluria alone.

Six of the 11 patients with renal disease had structural abnormalities of the urinary tract such as urethral stenosis, nephrectomy, renal atrophy, or nephrocalcinosis. Eight of these 11 patients had systemic illness such as hypertension, diabetes mellitus, or both. In the bladder bacilluria group, seven of the nine patients had no associated illness, whereas two had either hypertension or diabetes.

For in vitro tests, stock solutions containing 2,000 μg of cinoxacin per ml were prepared in phosphate buffer (pH 7), stored at -20 C, and used within 6 weeks. Minimal inhibitory concentrations (MICs) were determined for all isolates by the standard tube dilution method using tryptose phosphate broth. Minimal bactericidal concentrations (MBCs), 99.99% killing, were also determined.

Before initiation of treatment, a urinalysis and culture, complete blood count, renal function (creatinine and electrolytes), and liver function tests (serum bilirubin, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, and lactate dehydrogenase) were obtained. Patients were treated with 250 mg of cinoxacin orally every 6 h for 10 days. Between days 3 and 5 of treatment, blood for drug levels was drawn 2 and 6 h after a dose. At the same time, urine was collected for urinalysis and culture. Urine drug levels were determined on 2-h collections for a total of 6 h after the last dose. Drug standards were made in serum and pooled normal urine. These were stored at -20 C and used within 4 weeks. Drug levels were determined by an agar disk diffusion method using a susceptible strain of Escherichia coli (provided by Lilly Research Laboratories). Patients were examined on day 10 (at the end of treatment), and previously noted blood and urine tests were repeated. All patients were followed for at least 4 to 6 weeks after completion of therapy.

RESULTS

The organisms cultured from the urine of study patients were E. coli in fifteen, Klebsiella-Enterobacter in five, Proteus mirabilis in two, and Providencia in one. Three patients had mixed infections. These strains (shown by shaded areas in Fig. 1) were susceptible to cinoxacin in the range 2 to 64 μg/ml. Streptococci,
includes enterococci which emerged during treatment, were resistant (MIC > 250 μg/ml). The MICs of organisms from patients in this series were compared with the MICs from a larger number of strains tested in vitro that are described in another paper (1) as shown by the bars. The extended dotted lines described the range of MBCs from the two studies. The arrows indicate that no end point was reached for the MBC of those organisms. Figure 1 also shows that the peak 2-h serum levels ranged from <4.0 μg/ml to 14.8 μg/ml. The median peak serum level was 7.4 μg/ml in the patients with renal disease and 6.4 μg/ml in the bladder bacilluria group. The range of urinary concentration was 88 μg/ml to 925 μg/ml in the immediate 2-h period after a dose. The median of the 2-h level, however, was 525 μg/ml in the bladder bacilluria group, compared to 162 μg/ml in the group with renal involvement. Urinary concentrations in each patient always exceeded the MBC of the infecting organism. The average amount of cinoxacin recovered in 6 h after a 250-mg dose was 86 mg, or 34%. There was no significant difference in the mean serum values in the two groups.

Table 1. Characterization of study patients

| Criteria for localization | Pyelonephritis | Bladder bacilluria |
|---------------------------|----------------|-------------------|
| Pyelogram:                |                |                   |
| Normal                    | 1              | 3                 |
| Abnormal                  | 10             | 6                 |
| Not Done                  |                |                   |
| Flank pain/tenderness/dysuria | 6           | 0                 |
| Dysuria only              | 0              | 8                 |
| Antibody-coated bacteriuria | 4/4           | 0/2               |
| Persistent same strain with pyuria | 5         | 0                 |
| Associated diseases       |                |                   |
| None                      | 1              | 7                 |
| Genitourinary abnormalities | 6            | 0                 |
| Systemic disease          | 8              | 2                 |

* Criteria for inclusion in the study were bacilluria of >10⁸ organisms/ml (20 out of 20 patients); pyuria >25,000 leukocytes/ml (18 out of 20); dysuria and/or flank pain (14 out of 20).
* Eleven patients involved.
* Nine patients involved.

![Diagram](http://aac.asm.org/)

**Fig. 1.** Relation of in vitro susceptibility and drug levels. MICs of organisms isolated in this study are shown by the shaded area. The range of MICs and MBCs from a larger in vitro study (1) is shown by the bars and dotted lines, respectively. The arrows indicate an MBC greater than the corresponding value in micrograms per milliliter. In the lower portion of the figure are peak serum and urine levels in the patients with pyelonephritis (●) as compared to those with bladder bacilluria (○).
ment, 13 patients had sterile urine. In four patients, persistence or recurrence of the same strain occurred. The MICs of two of these four organisms changed from 4 to 16 μg/ml, whereas the other two were unchanged. Two patients had acquired a new bacillary infection, and one (previously noted) acquired infection with an enterococcus that persisted after treatment. The cure rate at 6 weeks was 80% for the initial infecting organism, but only 65% of the patients had sterile urine.

Data on quantitative pyuria (Fig. 2) was obtained to observe the effect of treatment on the inflammatory response to the urinary tract infection. Resolution of pathological pyuria occurred in all but one of the patients who obtained a bacteriological cure at 10 days and 6 weeks. In patients with a new or persistent infection at 10 days, pyuria persisted in four of eight patients. Of those who were infected at 42 days, six of seven had pathological pyuria.

**DISCUSSION**

Desirable features of a good antimicrobial in the treatment of urinary tract infections are a wide spectrum of activity against common causative pathogens, high urinary concentrations of the drug (4, 5), ease of administration, and freedom from side effects and toxicity. The *Enterobacteriaceae* in the study patients were susceptible to 2 to 64 μg/ml, although the streptococci, including enterococci which appeared in 35% of the patients during treatment, were resistant (MIC > 250 μg/ml). Their emergence is perhaps explained by selection of these resistant organisms from unnoticed low numbers in the urine at the outset of treatment. These gram-positive organisms, however, were present only transiently (and symptomatically) in all but one affected patient.

Although the urinary concentrations ranged from 88 to 925 μg/ml, these were, in each patient, higher than the MBC of the infecting organism. This is a significant advantage of cinoxacin. In only one case was a susceptible organism (*Providencia*) persistent in spite of adequate urine levels at 3 and 10 days. This patient had urethral stenosis and pyelonephritis, and cultures yielded the same organism several times. Urethral dilatation was done monthly and the persistant infection was thought to represent a focus of infection either in the kidney or prostate.

Relative to the in vitro antagonism of drug against *P. mirabilis* by glucose (1), none of the patients with *Proteus* infections had diabetes in this study. Hence, the inhibitory effect of glucose (i.e., increase in MIC with increasing concentrations of glucose) could not be tested. Also, the pH range of urine was too narrow to draw...
any firm conclusions about its effect on treatment.

Although clearance of cinoxacin appears to be influenced by renal function (decreased peak urine levels in patients with renal involvement), no valid conclusion can be made in the absence of data such as creatinine clearance or glomerular filtration rate. The fact that the average amount of cinoxacin recovered in the urine was 86 mg (or 34%) indicates that incomplete absorption, other routes of excretion, or inactive metabolites account for 66%. Probably because of the extra renal modes of drug excretion, the peak plasma level has no consistent relation to the serum creatinine.

There was no gastrointestinal, hematological, renal, or hepatic toxicity noted. One additional patient with renal insufficiency (who was dropped from the study because his initial strain was resistant to cinoxacin) had severe nausea, vomiting, and diarrhea concomitant with treatment. This subsided when treatment was discontinued. The peak and trough serum levels for this patient were the highest of the series (17.7 and 7.7 μg/ml, respectively).

In conclusion, cinoxacin appears to be a safe and useful drug in the treatment of urinary tract infections caused by Enterobacteriaceae. The previously described favorable features of the drug in vitro (1, 3) appear to be more important clinically than the antagonism, inhibitors, and other potentially adverse factors observed. The cure rate in this study was highly satisfactory. The drug was well tolerated and easy to use. The results suggest a useful role for cinoxacin in the treatment of urinary tract infections.

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