Treatment of Outpatient Urinary Tract Infections with Cinoxacin

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This paper describes an open assessment of cinoxacin in the treatment of 30 outpatients with symptomatic urinary tract infections caused by Escherichia coli, Klebsiella, Proteus mirabilis, and Enterobacter. Twenty-seven patients (90 percent) had a satisfactory clinical response and in 26 patients, there was a satisfactory microbiological response with elimination of the pathogen. Mild side effects were reported by three patients, none of whom stopped therapy. It is concluded that cinoxacin will be useful in the treatment of urinary tract disease because of the high urinary antibacterial activity produced. The relatively low incidence of side effects and convenience of twice-daily dosage should encourage good compliance by patients treated outside the hospital setting.

Cinoxacin is a synthetic cinnoline derivative in the same chemical class as nalidixic acid (NegGram) and oxolinic acid (Utibid), and has been shown to have activity against the gram-negative organisms that are most frequently isolated in urinary tract infections.[1,2] Studies in normal volunteers[3] and patients[4,5] showed that cinoxacin, given every 12 hours, produced urine concentrations that exceeded the minimal inhibitory concentration for 95 percent or more of the common gram-negative urinary pathogens.

Comparative studies in the treatment of patients with urinary tract infection have shown that cinoxacin was more effective than nalidixic acid and produced fewer side effects,[6] was as effective as nitrofurantoin while producing fewer side effects,[7] and was more effective than co-trimoxazole with a similar incidence of side effects.[8]

In order to gain experience with cinoxacin, the authors have undertaken, in two centers, an open study in which the admission of patients, diagnosis, microbiological examination, and symptomatic evaluation were carefully controlled.

Methods

Adult outpatients of either sex, 18 years or older, were admitted to the study if they were suffering from urinary tract infection but were otherwise in good health. The diagnosis was based on history and physical findings and confirmed by urine culture obtained no earlier than 24 hours prior to starting therapy. The microbiological evaluation included identification of the organism, colony count, and antimicrobial susceptibility using discs containing cinoxacin, 100 μg.

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Table 1. Distribution of Patients by Age and Sex

Sex	Age (years) <20	21-30	31-40	41-50	51-60	61-70	>70	Data Not Given	Total
Male	—	—	—	—	1	1	2	—	4
Female	3	5	3	2	4	3	5	1	26
Total	3	5	3	2	5	4	7	1	30

Table 2. Causative Organism, Disease Stage, and Class

Stage	Class	Organism: Escherichia coli	Proteus mirabilis	Enterobacter	Klebsiella	Enterobacter cloacae	Klebsiella and Enterobacter	Total
Initial	Complicated	2	—	—	—	1	—	3
	Uncomplicated	5	1	1	—	—	—	7
Recurrent	Complicated	8	1	—	1	—	1	11
	Uncomplicated	7	—	1	—	1	—	9
Total		22	2	2	1	2	1	30

Patients were excluded if the colony count was less than 100,000/ml, if the causative organism was subsequently shown to be resistant to cinoxacin, if they required treatment with a second antimicrobial drug, or if they had received successful antimicrobial therapy in the four days preceding the study. Pregnant patients were excluded, as were those who had known renal or hepatic impairment.

On admission to the study, and after the pretherapy urine culture had been taken, the patient started treatment with cinoxacin. Between the second and fourth days of treatment, another urine sample was obtained for microbiological culture, and a final culture was made five to nine days after treatment was completed. All patients took cinoxacin, 500 mg, twice daily for 13 to 15 days; side effects were recorded during the study, and laboratory monitoring of biochemistry, hematology, and urinalysis was performed before treatment, after one week of treatment, and five to nine days after treatment was completed.

Results

Forty patients were admitted to the study, but in ten, the microbiologic data were incomplete and therefore are not considered further. In the remaining 30 patients, 4 were male and 26 female, and their distribution by age and sex is shown in Table 1. Twenty-eight patients had a diagnosis of cystitis or lower urinary tract infection and two females had pyelonephritis. One male and 9 females had initial infections with no history of urinary tract infection in the previous 12 months, and 3 males and 17 females had recurrent infections, ie, one or more episodes of urinary tract infection in the past 12 months. Uncomplicated

Table 3. Response to Therapy

Stage	Class	Response				
		Clinical		Bacteriological		
		Satisfactory	Unsatisfactory	PE	RNP	RSP
Initial	Complicated	3	—	2	—	1
	Uncomplicated	7	—	7	—	—
Recurrent	Complicated	8	3	8	2	1
	Uncomplicated	9	—	9	—	—
Total		27	3	26	2	2

Key: PE=Pathogen eliminated
RNP=Reinfection, New Pathogen
RSP=Recurrence, Same Pathogen

infections were defined as infections that were not accompanied by structural abnormalities, neurological lesions, or medical disease conducive to infection. Uncomplicated urinary tract infections were seen in 2 males and 14 females, and complicated infections were recorded in 2 males and 12 females (Table 2).

Twenty-four patients were treated for 14 days, 2 patients were treated for 13 days, and 4 patients were treated for 15 days. Because of a misunderstanding, one patient took cinoxacin, 1 gm, twice daily, but the other 29 were treated with 500 mg, twice daily.

The effectiveness of treatment was assessed on clinical and microbiological response. A satisfactory clinical response was indicated by disappearance or improvement of the presenting signs and symptoms. If symptoms recurred during the period of post-therapy observation, an unsatisfactory response was recorded. A sterile urine culture five to nine days after treatment ended indicated that the pathogen had been eliminated. If patients had sterile urine during therapy but a post-therapy culture that grew the pathogen originally isolated, this was recorded as a relapse. If a new pathogen was present in the post-therapy culture, this was recorded as reinfection, new pathogen.

Twenty-seven patients had a satisfactory clinical response, but three with recurrent complicated infections had an unsatisfactory clinical response. Escherichia coli was the most common causative organism, identified in 22 patients (Table 2) and the microbiological evaluation at the end of treatment showed the pathogen was eliminated in 26 patients (Table 3). The original organism was still present in two patients, but both had a satisfactory clinical response. Two patients were reinfected with a new organism. Mild side effects were reported by three patients, none of whom stopped therapy. One patient complained of nausea and dizziness and one complained of nausea. The third patient complained of constipation but this could not definitely be attributed to cinoxacin.

The laboratory monitoring showed that six patients had a transient abnormality in liver function tests (SGOT, SGPT, alkaline phosphatase); two patients had changes in both SGOT and SGPT, but the remainder showed alteration in only one enzyme. One patient had abnormal alkaline phosphatase levels on two occasions. Three patients had an abnormal lymphocyte count and another patient had one abnormal hematocrit and red blood cell count. None of these changes were clinically significant.

Discussion

This study has confirmed the results of other investigators[9-11] who found that cinoxacin, 500 mg, twice daily, was effective in the treatment of uri-

nary tract infection caused by the common organisms such as E coli, Klebsiella, Proteus mirabilis, and Enterobacter. The clinical response was satisfactory in 27 of 30 patients (90 percent); the three failures occurred in patients with recurrent complicated infections that had already failed to respond to treatment with other antimicrobial drugs. The microbiological response was satisfactory, with elimination of the pathogen in 26 of 30 patients (87 percent); 2 patients with recurrent complicated infections were reinfected with a new pathogen and 2 patients with complicated infections had a recurrence with the same pathogen. The type and incidence (10 percent) were in agreement with reports from other studies.[8,11] Welles et al[11] reported the findings in 1,118 patients; 4.4 percent had adverse experiences and 5.5 percent had reactions that could not be related to cinoxacin. Hematology, blood chemistry, and urinalysis values were unaltered by cinoxacin administration in this study.[11] The side effects reported in our study are minor and have not been substantiated in other large studies. One could not attribute these minor changes in our determinations with certainty to cinoxacin. Cinoxacin is rapidly absorbed from the gastrointestinal tract. Peak serum levels occur two to four hours after ingestion.[12] The drug is well tolerated and excreted in patients with markedly impaired renal function.[12] As with other drugs, the safety of cinoxacin in pregnancy has not been established. Cinoxacin has been approved by the Food and Drug Administration for marketing, but as yet has not been released on the market.

It has been shown that successful therapy in urinary tract infection is related to antimicrobial activity within the urine[13] and that cinoxacin produces high urine concentrations[3-5] and high antimicrobial activity.[8] It has been shown[14] that urinary excretion of free drug in the 24-hour period following a single 500 mg dose of cinoxacin was 42 percent, compared with 11.3 percent after nalidixic acid, 500 mg, and 0.6 percent after oxolinic acid, 750 mg. The reason for development of resistance in these drugs may be due to these low excretion levels. Cinoxacin's high level of excretion should help to alleviate the problem of development of resistant organisms. The relatively low incidence or absence of side effects seen with other similar drugs and the convenience of twice-daily medication with cinoxacin, avoiding the necessity of taking the drug while the patient is at work or out of the house, should enhance compliance. This, coupled with the good results obtained in this study, suggests that cinoxacin is a very useful drug for the treatment of urinary tract infection caused by the susceptible gram-negative organisms.

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