Comparison of Low-Dose Cinoxacin Therapy and Placebo in the Prevention of Recurrent Urinary Tract Infections

William E. Scheckler, MD, Robert A.P. Burt, MB, ChB, and David F. Paulson, MD
Madison, Wisconsin, Indianapolis, Indiana, and Durham, North Carolina

Fifty-nine female patients with a history of at least three episodes of urinary tract infection in the preceding year were enrolled in a two-center, double-blind study comparing cinoxacin and placebo as preventive therapy. Evaluation of efficacy was based on the results from 41 patients for whom complete data were available. In the cinoxacin-treated group, 18 of 20 patients remained asymptomatic during the study, compared with 11 of 21 patients in the placebo group. This difference between the two treatment groups was significant ($P = 0.031$). One patient in the cinoxacin group and eight patients in the placebo group developed an infection during the study. This difference was also significant ($P = 0.045$). Nine patients spontaneously reported adverse reactions, four in the cinoxacin group and five in the placebo group. In four instances, these were sufficiently severe for the treatment to be withdrawn from one patient who received cinoxacin and three patients who received placebo. The results of this study have shown that cinoxacin was significantly more effective than placebo in preventing urinary tract infection in patients with a history of frequent recurrent infections.

It is now established that once-daily antimicrobial prophylaxis is effective in preventing recurrent urinary tract infections in women.[1] Studies have shown that nitrofurantoin and trimethoprim-sulfamethoxazole (TMP-SMX) can be used successfully,[1,2] but for those patients who have more than three episodes of infection per year, prophylaxis can be more cost effective than treating each episode separately.[3]

For an antimicrobial agent to be considered for prophylactic therapy, it must provide high urine concentrations of active drugs, be well tolerated by the patient, and not lead to the emergence of resistant strains of bacteria. While both nitrofurantoin and TMP-SMX fulfill these criteria and are currently the two most widely used drugs for this indication, a recent study has shown that nitrofurantoin can cause serious and sometimes fatal adverse effects.[4] Work in Britain has also shown that there has been a large increase in the organisms

Requests for reprints should be addressed to Dr. William E. Scheckler, Department of Family Medicine and Practice, Medical School, University of Wisconsin–Madison, Madison, WI 53715.

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showing trimethoprim resistance due to transferable R plasmids.[5,6] The frequency of allergic reactions to sulfa compounds is well known.

Cinoxacin (Cinobac) is a recently introduced synthetic antibacterial agent that produces mean urine concentrations higher than the mean minimum inhibitory concentration for most of the common urinary pathogens for 12 hours following a single 500-mg dose.[7] A comparative pharmacokinetic study showed that concentrations of free drug in the urine are higher for cinoxacin than either nitrofurantoin or TMP-SMX.[8] In an outpatient study of urinary tract infection, cinoxacin was shown to be effective and well tolerated by the patients.[9] In a comparison with TMP-SMX, cinoxacin was as effective but without the emergence of resistant bacteria associated with trimethoprim-sulfamethoxazole.[10] In vitro bacterial resistance has not been shown to be transferable via R factor.[11,12] Cinoxacin is unrelated chemically to sulfa drugs or nitrofurantoins and therefore could be used as an alternative if side effects develop.

For these reasons cinoxacin would seem to be a useful drug for prophylactic therapy. This paper describes a comparison with placebo in patients with a history of recurrent urinary tract infections undertaken at two centers, each using the same protocol.

Methods

This was a double-blind comparative study of cinoxacin, 500 mg administered once daily, and placebo. Female outpatients over 18 years of age were enrolled if they had a history of three or more urinary tract infections in the preceding year. Most patients had documentation of prior urinary tract infection by the presence of pyuria or more than 100,000 organisms per milliliter of urine. In a few cases classic symptoms of upper or lower tract disease were accepted as evidence of an infection episode in the previous year. At the time of enrollment all patients had a sterile urine and were in reasonably good health. Patients were excluded if they were pregnant, had indwelling catheters, or had a urine culture that grew more than 10,000 colonies per milliliter. Patients were also excluded if they were taking anxiolytic drugs or had another infection that required treatment. All patients gave their written, informed consent to take part in the investigation. Patients came from three family practice outpatient clinics and a general urology clinic.

Samples of clean-catch midstream urine were obtained for microbiologic culture within seven days and within 24 hours of starting treatment. Only if both cultures showed less than 10,000 colonies per milliliter was the patient enrolled in the study. Further cultures were made between the first and second week of treatment, between the third and fourth week, and each month thereafter. If any culture showed more than 10,000 colonies per milliliter and the patient was asymptomatic, a second culture was obtained. If the colony count was confirmed, then the patient was withdrawn from the study. At two weeks and one month after stopping therapy, further cultures were obtained. Discs containing 100 μg of cinoxacin were used for the in vitro susceptibility testing.

The cinoxacin and placebo were supplied in opaque white capsules of identical appearance, and the patients took one capsule, either 500 mg of cinoxacin or placebo, once daily for six months. The order of drug administration was determined by random code. Drug compliance was assessed by capsule counts and interviews at the monthly follow-up visits.

Assessment of efficacy was based on symptomatic evaluation: "satisfactory," or "unsatisfactory" if the patient developed any signs or symptoms that indicated the occurrence of urinary tract infection. Bacteriologic evaluation was based on the presence or absence of organisms, colony counts, and in vitro susceptibility. Routine laboratory monitoring was undertaken prior to the first dose of study drug, at regular intervals throughout the trial, and at the end of the study. Adverse drug reactions that were spontaneously volunteered or elicited in response to nonspecific questioning were recorded, and their association with the study drug identified. All patients were given a complete ophthalmologic examination at the beginning and end of the study.

Results

A total of 59 female patients were enrolled in the study. Thirty were treated with cinoxacin and 29 received placebo; the age distribution in the two treatment groups is shown in Table 1. Of the 59 patients enrolled, 41 fulfilled all the protocol re-

Table 1. Distribution of Female Patients by Treatment Group and Age

	Age (yr)					
	18-25	26-35	36-45	46-55	56-65	Total
Treatment Group						
Cinoxacin	12	14	3	0	1	30
Placebo	12	11	1	2	3	29
Total	24	25	4	2	4	59

Table 2. Treatment Failures, Showing Duration of Treatment, Clinical and Bacteriologic Response, and Infecting Organisms

Treatment	Days Treated	Symptomatic Response	Bacteriologic Count (per mL)	Organisms
Cinoxacin	209	PDS	50,000	Mixed gram-positive
	15	PDS	100,000	E coli
Placebo	41	PDS	100,000	Enterococci
	40	PDS	100,000	E coli
	75	PDS	100,000	E coli
	111	PDS	100,000	Klebsiella, E coli
	30	PDS	100,000	E coli
	146	PDS	100,000	E coli
	206	PDS	60,000	Mixed gram-positive
	180	PDS	100,000	Mixed gram-positive
	169	PRA	100,000	E coli

PDS—Patient developed symptoms
PRA—Patient remained asymptomatic

quirements and provided complete clinical and microbiologic data. Twenty of these patients received cinoxacin, and 21 received placebo. The evaluation of drug efficacy was based on the data from the 41 patients, but information from all 59 patients was included in the assessment of adverse reactions. Nine patients were excluded because they had been treated for fewer than 50 days, three for poor compliance, four because bacteriologic cultures were not obtained as specified in the protocol, and two for other protocol violations.

In the cinoxacin-treated group, 18 of the 20 patients remained asymptomatic for the duration of the study; the shortest period of treatment was 159 days and the longest was 220. One patient developed symptoms after being asymptomatic for 209 days, and urine culture showed mixed gram-positive organisms with a count of 50,000 colonies per milliliter. One patient developed symptoms after 15 days of treatment; urine culture showed Escherichia coli, susceptible to cinoxacin, and a count of 100,000 colonies per milliliter (Table 2). Microbiologic cultures throughout the period of treatment showed that, except for the two described above, all patients had sterile urine or colony counts less than 10,000/mL. In the placebo-

treated group, 11 of the 21 patients remained asymptomatic during the study. The shortest period of treatment was 54 days and the longest was 213 days. The symptomatic response was not recorded for two patients, but in both instances, the microbiologic cultures showed sterile urine or colony counts below 10,000/mL.

Six patients developed symptoms and had more than 100,000 colonies per milliliter on culture. Two patients developed symptoms with colony counts less than 10,000/mL, and one patient remained asymptomatic with a urine culture of more than 100,000 colonies per milliliter. These results are shown in Table 2. Using Fisher's Exact Test, the difference between the number of patients remaining asymptomatic in the two treatment groups was significant ($P = 0.031$). The same test showed that the differences in microbiologic failure in the two groups were also significant ($P = 0.045$). All 59 patients were included in the assessment of adverse drug reactions, which were reported by 4 patients in the cinoxacin group and 5 patients in the placebo group. Treatment was discontinued in four patients because of these reactions, but the other patients reported the reaction on one occasion during the study and continued with therapy. Three patients complained of two or more reactions, and one patient in the placebo group was found to have an elevated SGOT and serum bilirubin level during the study, but continued with the treatment. No ophthalmologic abnormalities were found at the beginning or end of the study.

Discussion

The results of this study confirm the findings of others that the administration of a single daily dose of an antibacterial drug to patients with a history of recurrent urinary tract infections will provide effective prophylaxis as long as the treatment is continued. In this study, the symptomatic failure rate was 2 in 20 and the bacteriologic failure rate was 1 in 20 in the group treated with active drug. These figures agree closely with those of Stamm and his colleagues.[1] On the other hand, the symptomatic failure rate in the placebo treatment group was 8 in 19 (symptomatic data were missing from two patients) and the bacteriologic failure rate was 8 in 21. These failure rates in placebo-treated patients are similar to those previously reported.[1,13] Because of the previously discussed side effects of other agents, cinoxacin is a rational alternative prophylactic agent in appropriate patients. Preliminary data suggest rapid development of resistance will not be a problem. However, since the drug has only been on the market for one year, it may be premature to predict resistance potential. The rate of side effects in the placebo group confirms the value of the double-blind placebo-control group methodology when studying a new drug. This study has demonstrated that cinoxacin in a single 500-mg daily oral dose is an effective prophylactic agent for adult women with recurrent urinary tract infections.

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