ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1973, p. 593-596

Vol. 4, No. 6
Printed in U.S.A.

Double-Blind Comparison of Carbenicillin Indanyl Sodium, Ampicillin, and Cephalexin in Treatment of Urinary Tract Infection

KRISTEN M. RIES, C. GLENN COBBS, JAY Y. GILLENWATER, MATTHEW E. LEVISON, GERALD L. MANDELL, MERLE A. SANDE, AND DONALD KAYE

Department of Medicine, University of Alabama Medical School, Birmingham, Alabama 35233, Department of Medicine, The Medical College of Pennsylvania, Philadelphia, Pennsylvania 19104, and the Departments of Medicine and Urology, The University of Virginia School of Medicine, Charlottesville, Virginia 22204

Received for publication 24 July 1973

Carbenicillin indanyl sodium, ampicillin, or cephalexin was administered orally to 61 patients with urinary tract infections. Assignment of drug was made by a computer-generated, randomized plan in a double-blind fashion. The rates of cure 4 weeks after therapy were 50, 42, and 50% for patients treated with carbenicillin, ampicillin, and cephalexin, respectively. Failure of therapy was correlated with chronicity of infection and sensitivity of the microorganism to the antibiotic used. Thirty-nine percent of the patients developed side effects, but there were no significant differences in side effects among the three antibiotics. This double-blind study demonstrates that carbenicillin indanyl sodium is as effective as ampicillin and cephalexin in treatment of urinary tract infections.

Carbenicillin indanyl sodium is an indanyl ester of carbenicillin which is absorbed after oral administration, and once absorbed it is rapidly hydrolyzed to carbenicillin (2). Recently several studies have demonstrated that the indanyl ester of carbenicillin is effective in the treatment of urinary tract infections (1, 3, 4). A previous single-blind study by the authors showed that carbenicillin indanyl sodium was as effective as ampicillin and cephaloglycin in treatment of urinary tract infections (3).

The purpose of this study was to compare the indanyl ester of carbenicillin with oral ampicillin and cephalexin in treatment of patients with urinary tract infections by using a randomized plan of patient assignment in a double-blind fashion.

MATERIALS AND METHODS

Patients. Sixty-one patients (11 men and 50 women) with urinary tract infections were studied at the Hospital of the Medical College of Pennsylvania, the University of Virginia Hospital, and the University of Alabama Hospital and Clinics from December 1972 to February 1973.

Criteria for inclusion in the study were as follows: (i) in asymptomatic patients, two or more quantitative urine cultures on different days demonstrating at least 10^5 of the same bacteria per ml of urine or in symptomatic patients, one culture with at least 10^5 bacteria per ml; (ii) no other antimicrobial therapy or instrumentation of the urinary tract during the period of study and follow-up; and (iii) no known allergies to the penicillins or cephalosporins, or both.

The following determinations were made before and after therapy: urinalysis, complete blood count, blood urea nitrogen, and serum creatinine, alkaline phosphatase, bilirubin, and glutamic oxaloacetic transaminase. Quantitative urine cultures were obtained during day 2, 3, 4, 5, or 6 of therapy, at the end of therapy, and 2 and 4 weeks after completion of therapy.

Intravenous pyelograms were obtained in 12 patients. The classification as to acute or chronic infection was made according to the duration of the infection and changes on intravenous pyelogram. Patients with symptoms for fewer than 3 weeks and with no roentgenographic changes of pyelonephritis were considered to have acute infection. Patients with symptoms for longer than three weeks and with roentgenographic changes of pyelonephritis or with asymptomatic bacteriuria were considered to have chronic infection.

Urine cultures. Urine for culture was a midstream specimen obtained after cleaning and drying the perineum and external urethra. Each specimen was processed immediately or after several hours of refrigeration at 4 C. Quantitative cultures of urine were performed by streaking 0.01 and 0.001 ml of urine on blood agar plates by using calibrated loops. The number of bacteria per milliliter was calculated from the number of bacterial colonies developing after incubation of the plates for 24 h at 37 C.

Therapy. Either carbenicillin indanyl sodium (500 mg four times per day); ampicillin (500 mg four times per day); or cephalexin (250 mg four times a day) (all orally) was assigned to a patient by a computer-generated randomized plan before the antimicrobial susceptibilities of the infecting microorganism were known. Each drug was administered in identical-appearing capsules for the purpose of the double-blind comparison. The doses used were those recommended by the manufacturers. Therapy was continued for 4 to 14 days except (i) if toxic side effects forced discontinuation or (ii) if the urine culture during therapy demonstrated 10^5 or more microorganisms per ml of urine.

The results of therapy were classified as: (i) cure, when urine cultures were negative ($< 10^4$ bacteria per ml) during therapy and at follow-up; (ii) cure with reinfection, when urine cultures were negative during therapy but when reinfection ($\geq 10^5$ of a new organism per ml of urine) was noted 2 to 4 weeks after stopping therapy; (iii) persistence, when 10^5 or more of the initial infecting organism were found in the urine during therapy; (iv) superinfection, when reinfection developed during therapy; and (v) relapse, when 10^5 or more of the original infecting organisms per ml of urine were present at follow-up, after demonstration of less than 10^4 per ml on all cultures taken during therapy. *Escherichia coli* strains were serotyped to help differentiate between relapse and reinfection.

In vitro antibiotic susceptibility sensitivity tests. Susceptibilities of infecting microorganisms to disodium carbenicillin, ampicillin trihydrate, and cephalexin monohydrate were determined by an antibiotic dilution method in heart infusion broth at pH 7.4. The antibiotics were diluted in twofold steps in tubes containing 0.5 ml of broth. The inoculum for each tube was 0.5 ml of a 10^{-4} dilution of an 18-h culture of each strain in heart infusion broth at pH 7.4. The tubes were incubated at 37 C for 24 h and examined for turbidity. The minimal inhibitory end point was considered to be the minimal concentration of antibiotic that prevented turbidity.

RESULTS

Patients. Sixty-one patients were studied; 20 received carbenicillin indanyl sodium, 19 received ampicillin, and 22 received cephalexin.

Table 1 shows the age, sex, and classification (as to acute or chronic) of the infections in each group of patients. Four male and 16 female patients were treated with carbenicillin, 2 males and 17 females were treated with ampicillin, and 5 males and 17 females were treated with cephalexin. There were no significant differences ($P > 0.05$) in sex distribution, age, or the number of patients with acute or chronic infections among the three groups.

Infecting microorganisms. Table 2 lists the infecting microorganisms for each of the groups. There were no significant differences ($P > 0.05$) among the three groups as to proportion of *E. coli* or any other organisms.

Figure 1 shows the minimal inhibitory concentrations of carbenicillin, ampicillin, and cephalexin for 58 of the infecting microorganisms. All three antibiotics were active against most of the organisms; 76 to 88% were inhibited by 31 μg of each drug per ml, concentrations easily achieved in the urine.

Results of therapy. The results of therapy are listed in Table 3. Twenty-nine of the 61 patients (48%) treated with carbenicillin, ampicillin, or cephalexin became abacteriuric during therapy and remained abacteriuric during the entire follow-up period. There were no significant differences among the three groups in cure rates (even with "cure with reinfection" included as cures). Superinfection occurred in two patients in the carbenicillin group and one patient in the ampicillin group.

Twenty-four (39%) of the patients developed side effects during therapy; 8 patients were receiving carbenicillin, 10 patients were receiving ampicillin, and 6 patients were receiving cephalexin. Nine (38%) of the 24 patients developed more than one side effect. All individual side effects are listed in Table 4. No other toxic effects (e.g., hematopoietic, renal, hepatic) other than those listed in Table 4 were observed. Nausea and vomiting of a severe enough degree

TABLE 1. *Age, sex, and chronicity of infection*

Determination	Carbenicillin (20 patients)		Ampicillin (19 patients)		Cephalexin (22 patients)	
	No.	%	No.	%	No.	%
Mean age (years)	39		37		43	
Age range (years)	16–80		20–81		20–77	
Males	4	20	2	11	5	23
Females	16	80	17	89	17	77
Acute infections (symptoms <3 weeks and no roentgenographic changes of pyelonephritis)	9	45	14	74	17	77
Chronic infections (symptoms >3 weeks; asymptomatic bacteriuria or roentgenographic changes of pyelonephritis)	11	55	5	26	5	23

TABLE 2. *Infecting microorganisms*

Organism	Carbenicillin		Ampicillin		Cephalexin	
	No.	%	No.	%	No.	%
Escherichia coli	13	65	11	58	11	50
Klebsiella pneumoniae	4	20	2	11	2	9
Proteus mirabilis	0		2	11	4	18
Pseudomonas	0		0		1	5
Others	3	15	4	21	4	18

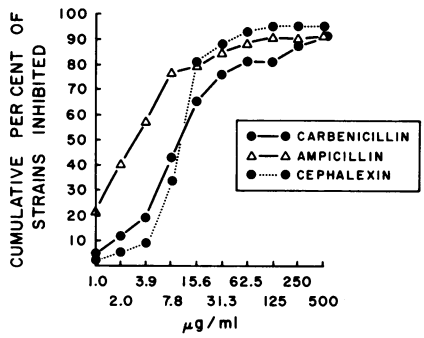

FIG. 1. *Minimal inhibitory concentrations of disodium carbenicillin, ampicillin trihydrate, and cephalexin monohydrate for 58 of the infecting microorganisms.*

TABLE 3. *Results of therapy*

Result	Carbenicillin		Ampicillin		Cephalexin	
	No.	%	No.	%	No.	%
Cure	10	50	8	42	11	50
Cure with reinfection	2	10	1	5	3	13
Persistance	3	15	1	5	1	5
Relapse	2	10	6	32	7	32
Superinfection	2	10	1	5	0	
Discontinued because of side effects	1	5	2	11	0	

to cause therapy to be withdrawn occurred in one patient receiving carbenicillin and in one patient receiving ampicillin. The patient who had severe nausea and vomiting while on ampicillin received ampicillin later without similar effects. Ampicillin had to be discontinued in one patient because of severe diarrhea. Otherwise, diarrhea was usually only of a mild degree in all three groups.

Factors related to failure of therapy. Figure 2 illustrates the minimal inhibitory concentrations of carbenicillin for the strains isolated from patients treated with carbenicillin, ampicillin, and cephalexin. Strains from patients who were cured and strains from patients who were not cured are plotted separately. There was a high correlation between success of therapy and susceptibility of the infecting organism to carbenicillin, with less striking correlations for ampicillin or cephalexin. Ninety percent of the strains from patients cured with carbenicillin were inhibited by 62.5 μg of carbenicillin per ml, whereas only 55% of strains from patients that were not cured were inhibited by 62.5 μg/ml. Patients with infections caused by organisms resistant to 500 μg or more of carbenicillin, 7.8 μg of ampicillin, or 62.5 μg of cephalexin per ml were not cured.

In all five patients in whom infection persisted, the infecting microorganism was highly resistant to the antibiotic given. Thirteen of the patients who relapsed were infected with organisms that were susceptible to the treatment antibiotic; none of the relapse stains changed in susceptibility to the antibiotic that was administered.

There was a correlation of chronicity of infec-

TABLE 4. *Side effects of antimicrobial therapy*

Side Effects	Carbenicillin (8)[a]	Ampicillin (10)[a]	Cephalexin (6)[a]
Nausea and/or vomiting	2	3	2
Diarrhea	1	5	2
Eosinophilia	1	2	3
Rash	1	2	0
Others (drowsiness, bad odor, bitter taste, lightheadedness, edema of hands, decreased hematocrit, increased alkaline phosphatase)	5	2	2

[a] Number in parentheses is number of patients.

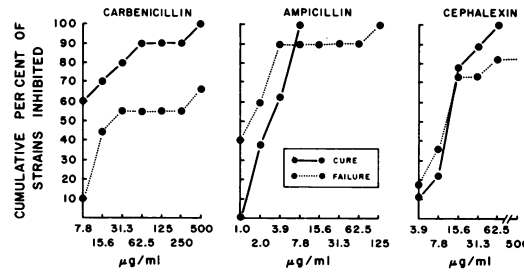

FIG. 2. *Minimal inhibitory concentrations of disodium carbenicillin, ampicillin trihydrate, and cephalexin monohydrate for the infecting microorganisms in patients treated with these three drugs, respectively. Strains from patients who were cured are represented by solid lines, and strains from those who were unsuccessfully treated are represented by the broken lines.*

tion with failure of therapy. Twenty-two of 40 patients (55%) with acute infections were cured; whereas 7 of 21 patients (33%) with chronic infections were cured. However these differences were not significant ($P > 0.05$).

DISCUSSION

The present double-blind study demonstrated that, in the patient population studied, there were no significant differences between carbenicillin indanyl sodium, ampicillin, and cephalexin in cure rates of urinary tract infection or in toxic side effects.

These results agree with a former single-blind study by the same authors in which no significant differences were found between carbenicillin indanyl sodium, ampicillin, and cephaloglycin in treatment of urinary tract infection (3). In that study 1 g of carbenicillin indanyl ester was given four times a day, and the usual dose of ampicillin was 1 g four times a day; in the present study the doses of carbenicillin indanyl ester and ampicillin were 500 mg four times a day. Although the cure rates in the present study with lower doses of carbenicillin and ampicillin were higher than in the previous study (50 and 42%, respectively, as compared with 33 and 32%), they were not statistically significantly different ($P > 0.05$ for both).

ACKNOWLEDGMENTS

The technical assistance of Kathleen King, Evan Zimmer, Kip B. Courtney, and Elizabeth K. Phillips is gratefully acknowledged. We are indebted to Marvin A. Turck and Clair E. Cox for serotyping of *E. coli* strains.

This study was supported in part by a grant from Chas. Pfizer and Co., Inc.

LITERATURE CITED

1. Bran, J., D. M. Karl, and D. Kaye. 1971. Human pharmacology and clinical evaluation of an oral carbenicillin preparation. Clin. Pharmacol. Ther. **12**:525-530.
2. English, A. R., J. A. Retsema, V. A. Ray, and J. E. Lynch. 1972. Carbenicillin indanyl sodium, an orally active derivative of carbenicillin. Antimicrob. Ag. Chemother. **1**:185-191.
3. Ries, K. M., C. G. Cobbs, J. Y. Gillenwater, M. E. Levison, G. L. Mandell, and D. Kaye. 1973. Comparison of carbenicillin indanyl sodium in treatment of urinary tract infections. J. Infect. Dis. **127**(suppl):S148-S153.
4. Wallace, J. F., E. Atlas, D. M. Bear, N. K. Brown, H. Clark, and M. Turck. 1971. Evaluation of an indanyl ester of carbenicillin. Antimicrob. Ag. Chemother. 1970, p. 223-226.