Double-Blind Comparison of Cephacetrile with Cephalothin/Cephaloridine

GEORGE GEE JACKSON, LOUISE J. RIFF, VICTORIA M. ZIMELIS, MOHAMMAD DAOOD, AND MOHAMMAD YOUSSEF

Department of Medicine, Abraham Lincoln School of Medicine, University of Illinois College of Medicine, and the Veterans Administration West Side Hospital, Chicago, Illinois 60680

Received for publication 8 November 1973

Under double-blind protocol, a controlled comparison was made between a new cephalosporin, cephacetrile, and cephalothin or cephaloridine. The patient's primary physician determined the indications for treatment, and the dosage was uniform for each route of administration. Infecting strains of staphylococci and *Proteus mirabilis* had a lower median inhibitory concentration for cephalothin than cephacetrile; the opposite was true for *Escherichia coli* and *Klebsiella* species. The average peak serum level 1 h after a dose of 2 g intravenously was 74.9 ± 21 and 21.5 ± 8.7 $\mu\text{g/ml}$ for cephacetrile and cephalothin, respectively; 6 h after the dose, the respective levels were 12.4 ± 4.3 and 3.7 ± 0.9 $\mu\text{g/ml}$. Renal clearances were similar and the plasma clearance was proportional to the serum levels. In the urine, the concentration of cephacetrile was three times higher than that of cephalothin. Based on a percentage of therapeutic potential, success in the treatment of infections with susceptible organisms was 42 and 44% for the two different drug regimens. Initial bacterial resistance was found in about one-fifth of infections, and concomitant therapy with other drugs was practiced in one-half of the treatment courses. Intravenous use of cephacetrile was discontinued prematurely more often than was use of cephalothin, suggesting less tolerance. Although there was no overt toxicity, more than 75% of patients on either regimen had some form of unwanted response to treatment, the most common being superinfection. From this limited but controlled experience, cephacetrile can be considered comparable to cephalothin in antimicrobial treatment and overall side reactions.

The clinical introduction of new drugs of the same class as others already licensed and established in clinical practice poses problems in evaluation. One approach is to treat enough patients with the new drug to determine that it is effective as therapy for certain types of infections without regard for its relative worth. In the case of most new antibiotics, the effect of closely related drugs with similar in vitro activity would be difficult to differentiate in clinical practice. There may be exceptions if there are marked differences in the in vivo bioavailability of one of them or if a very large experience is gained which gives significance to minor clinical differences. Nontherapeutic differences, such as toxicity, pain, acceptability, and ease of use of the drugs, may be easier to ascertain. In all of these regards, the ideal investigation would be a double-blind study of sufficient scope to match the effectiveness of the new agent against the standard established drug(s).

In this context, the clinical investigation of a

new cephalosporin, cephacetrile, was undertaken in a double-blind design in comparison with the related licensed drugs, cephalothin and cephaloridine. The format was a nonexclusive case study of patients for whom cephalosporin was prescribed by a primary ward physician. The clinical course and bacteriological results obtained in the treated patients were carefully monitored, adverse reactions were noted, and the relative in vivo pharmacokinetics of the drugs was measured.

MATERIALS AND METHODS

Adult medical and surgical patients were studied. The criterion for eligibility was prescription of a parenteral cephalosporin antibiotic by the primary physician. Before treatment, all patients were seen by one of the physician investigators for clinical evaluation and to obtain informed consent because the drug was to be used under blind code. The only exclusions from the study were patients who had received an initial dose of a licensed cephalosporin in the emergency, operating, or recovery room, and patients who

had received oral cephalosporin before admission. Some characteristics of the patients and treatment are given in Table 1.

Bacterial cultures from each patient were obtained at the beginning of therapy and every 2 to 5 days during treatment. The strains were speciated by standard microbiological methods. Tests for susceptibility to cephacetrile and cephalothin were performed by the serial twofold dilution technique using tryptose phosphate broth and an inoculum of 10^{-3} dilution of an overnight growth of a pure subculture which, after dilution, contained 10^5 to 10^6 /ml.

A random number table, in a proportion of 2:1 cephalothin to licensed cephalosporin, was used to select the medication for each patient admitted to the study. The assignment, by code, was made by the Hospital Pharmacy Investigational Drug Section. Medication was dispensed in specially prepared vials which were labeled with the patient's name, code number, time, date, and hospital location and stated

that the vial contained a specified weight of cephalosporin antibiotic for intravenous (i.v.) (or, alternatively, intramuscular [i.m.]) use. The code was known only to the Investigational Drug Section. Intravenous medication was given as 2 g of drug in a rider of saline or 5% dextrose infused over 30 min every 6 h. Two patients were treated only with i.m. medication in a dose of 0.5 g every 6 h. For most patients, treatment was given for 1 week or longer, with an average daily dose of 6 to 8 g. Some overlapping concurrent treatment with an aminoglycoside antibiotic was given in 14 of the courses; penicillin, erythromycin, or lincomycin was given in 8 courses, and rifampin was given once.

Six-hour urine collections between two doses, and blood samples taken 1 and 6 h after a dose, were obtained on day 2 of therapy or later to determine antibiotic concentration in urine and serum. The measurements were made by using a modified agar gel diffusion technique (7, 11) with *Bacillus subtilis*

TABLE 1. Characteristics of the study patient population

Condition	Patient group and treatment ^a						
	I		II (CA)	III		IV	
	CA	CL		CA	CL	CA	CL
No. observed	7	2	9	12	11	3	4
Avg age (years)	69	45	51	52	48	52	37
Range	(31-81)	(33-56)	(32-69)	(18-85)	(18-64)	(52-56)	(22-58)
Associated diseases							
Adrenal insufficiency					1		
Aplastic anemia or pancytopenia ...	1		1				
Benign tumor				1			
Bowel obstruction					1		
Carcinoma, sarcoma, melanoma, leukemia	2	1	1	3	2		
Chronic obstructive lung disease ...			1	1			
Cirrhosis and/or liver disease					2		
Coma-alcohol or hepatic	2						
Diabetes	2						
Heart failure, infarction		1	1				
Hemorrhage	2						
Nephrostomy or extrophy			1		1		
Occlusive vascular disease				3	1	2	3
Paraplegia				1			
Polyarteritis					1		
Post-op or fracture			2		3	3	4
Ulcerative colitis					1		
Uremia	1	1					
Days of treatment							
Average	4.7	7	4.3	9.6	9.7	2	1.5
Range	(1-11)	(1-13)	(3-6)	(7-17)	(7-14)		
Total dose							
Average	26.4	30.5	30.9	55.1	67.8	10.5	6.8
Range	(2-91)	(4-57)	(24-38)	(28-80)	(29-96)	(7-16)	(2-14)

^a Abbreviations: CA, cephacetrile; CL, cephalothin. Groups I, II, III, and IV are groups of patients who died and who received incomplete treatment, complete treatment, or prophylaxis, respectively.

(ATCC 6633) spores as the indicator organism. The serum specimens were assayed against standards in pooled serum, and the urines were assayed against standards in phosphate buffer. At the beginning of drug treatment, every 2 to 5 days during treatment, and at its completion, all patients had laboratory evaluations of hematological, renal, and hepatic functions.

To evaluate and compare the results of different treatment in series of patients that were not matched with adequate numbers in some subcategories, a percentage of therapeutic potential (PTP) achieved was calculated. Each patient was scored numerically: cure (eradication of the primary infecting organism with or without clinical recovery) = 3; improvement (marked clinical benefit with a decrease in the quantity of microbial growth) = 2; transient improvement (temporary loss of the infecting strain with rapid return during or immediately after treatment) = 1; failure (persistence of the infecting strain) = 0; and penalty failure (death caused by infection with a susceptible bacterial strain) = -3. The base of therapeutic potential was considered the cure of all patients or three times the number observed. Some patients who died were evaluated as having been cured of the infection, whereas two who died with failure to eliminate a susceptible bacterial strain from the blood after more than 24 h of treatment were considered penalty failures regardless of associated diseases.

RESULTS

Forty-six patients were given 48 courses of cephalosporin therapy. The in vitro susceptibilities of bacterial isolates recovered from them are compared for the two major drugs in Table 2. Nearly all strains of the species of gram-positive cocci tested were highly suscepti-

ble. Cephacetrile was less active than cephalothin against staphylococci, but all isolates were well within the therapeutic range. Among gram-negative bacilli, *Proteus mirabilis* was the most sensitive species, and cephacetrile was less active than cephalothin. *Escherichia coli* and *Klebsiella* species were of intermediate sensitivity. For each, cephacetrile was more active than cephalothin. A few strains of *Klebsiella* bacilli were highly resistant to both drugs. Most strains of *Enterobacter* species were quite resistant, as were all strains of *Pseudomonas aeruginosa*.

Seventeen of the 41 therapeutic courses, or 41%, were for urinary tract infections; septicemia, pneumonia, empyema, wound infections, and abscesses were the other indications. Eight of the 28 courses of cephacetrile and 4 of the 13 courses of cephalothin/cephaloridine were considered to provide no therapeutic test, owing to the initial resistance of the etiological bacterial strain, or because the cause was undetermined or the primary physician used concurrent therapy with another potentially effective antibiotic. The remaining cases in which the infecting organism was known to be susceptible and the result was not obscured by other treatment were evaluated by clinical and bacteriological analysis. For any condition where there were several patients, different degrees of success or failure of the same treatment regimen were observed. Some individual cases showed striking success or failure, but they did not provide a comparable basis against which to assess the comparison drug. To make a compar-

TABLE 2. Susceptibility of bacterial isolates

Species	No. tested	Test drug ^a	No. of strains inhibited (MIC; $\mu\text{g/ml}$) ^b													Median MIC ($\mu\text{g/ml}$)	Inhibited by avg serum concn (%)	
			≤ 0.25	0.5	1.0	2.0	4.0	8.0	16	32	64	128	256	≥ 500	Trough		Peak	
Streptococci and pneumococci	7	CA	6	1											<0.25	100	100	
		CL	6			1									<0.25	100	100	
Staphylococci	5	CA	1	2	1		1								0.43	100	100	
		CL	4		1										<0.25	100	100	
<i>Proteus mirabilis</i>	15	CA						2	4	8	1				19.0	20	89	
		CL				1	2	4	6	1		1			8.7	54	100	
<i>Escherichia coli</i>	23	CA					2	6	9	5	1				10.7	35	100	
		CL						4	4	6	7	2			24.0	0	44	
<i>Klebsiella</i> sp.	13	CA				1	1	5	1	1	1			3	7.6	54	77	
		CL					1	4	1	2	1	1		3	20	8	51	
<i>Enterobacter</i>	5	CA							1		1	1	1	1	96	0	43	
		CL									2	1	1	1	96	0	0	
<i>Pseudomonas</i>	7	CA												7	> 500	0	0	
		CL												7	> 500	0	0	

^a CA, Cephacetrile; CL, cephalothin.

^b MIC, Minimal inhibitory concentration.

ison of the relative value of each kind of treatment in the overall experience, a PTP obtained was calculated, as defined under Materials and Methods. On this basis, cephacetrile and cephalothin/cephaloridine were 42 and 44% effective, respectively, relative to the potential for cure in the patients treated. In this calculation, however, two penalty failures with cephacetrile in septicemia were included, whereas no septicemic patients were in the cephalothin treatment group.

In Table 3, the results of treatment are shown according to the clinical conditions for which therapy was given. Some sizeable differences are apparent in the observed PTP, but owing to the small numbers of cases the differences have no statistical significance. In general, cephacetrile tended to be more effective against gram-negative bacilli, both in the urinary tract and in tissue infection. When all gram-negative bacillary infections were lumped except those from septicemia, where there was no test sample with cephalothin treatment, the PTP achieved was 58 versus 33% for cephacetrile and cephalothin, respectively. Against staphylococci, streptococci, and pneumococci, the sample was very small, owing to the elimination of cases obscured by concurrent treatment with other effective drugs. However, one cephacetrile failure occurred in a patient who died with a persistent beta-hemolytic streptococcal bacteremia.

Measurements of the peak and trough concentrations of cephacetrile and cephalothin in blood samples taken at specified times after a given dose from individual patients on the 3rd to 6th days of treatment are shown in Fig. 1. The peak level varied greatly among patients, but in nearly all of them it was higher after a dose of cephacetrile than after the same dose of cephalothin. The order of difference was fourfold or greater in about one-third of the patients, threefold higher in another third, and zero to twofold in the remaining third. The trough level, 6 h after the dose, was also

variable, and in most patients it showed a marked decrease, usually fourfold or more relative to the peak concentration in the same person. Six hours after i.v. cephalothin, the trough levels were lower than those in most persons on cephacetrile. A small number of observations in persons with azotemia showed higher average trough levels, as expected. After i.m. administration of one-quarter of the i.v. dose of cephacetrile, the peak serum concentration was proportionately lower and the level at the trough was relatively better sustained.

The average peak serum concentration on a dose of 2 g given i.v. every 6 h in persons without azotemia was 74.9 ± 21 (standard deviation [SD]) $\mu\text{g/ml}$ with cephacetrile and 21.5 ± 8.7 (SD) $\mu\text{g/ml}$ with cephalothin. The respective trough levels for cephacetrile and cephalothin were 12.4 ± 4.3 (SD) and 3.7 ± 0.9 (SD). In Fig. 2, these are plotted graphically to show that the rate of plasma clearance between 1 and 6 h after a dose was proportional for the two drugs as a doubling function of the serum level. For each drug, the concentration at the 1st hour decreased by 83% by the 6th hour. Thus, the net total plasma clearance, including drug inactivation, was relatively the same for cephacetrile and cephalothin during this period, but at different levels.

In Table 4, the concentrations of each drug in the urine are given with data on the urinary excretion and renal clearance where measured. Cephacetrile attained concentrations in the urine that were three times greater than with the same dose of cephalothin. The extrarenal excretion (and degradation) of cephalothin was 2.7 times greater than for cephacetrile, whereas the renal clearance of the two was nearly the same. Higher urine concentrations of cephacetrile were obtained because of the higher plasma concentrations compared with cephalothin.

In Table 5, the four categories of patients that were discerned after treatment are presented. Owing to the design, there were 31 courses of

TABLE 3. Results of treatment with cephacetrile or cephalothin/cephaloridine

Treatment diagnosis	Treatment and result							
	Cephacetrile (i.v. or i.m.)				Cephalothin (i.v.) and cephaloridine (i.m.)			
	Cure	Improvement	Fail	PTP ^a	Cure	Improvement	Fail	PTP
Urinary tract infection	3	3	1	67	2	1	3	34
Septicemia	1	2	2 ^b	7		No test		
Tissue infections	1	4	3	48	1	1	1	56

^a Percentage of therapeutic potential.

^b Died of bacteremia with susceptible strain (penalty failure).

FIG. 1. Peak and trough serum levels of cephalosporins in individual patients.

FIG. 2. Proportionality of the net clearance of cephradine and cephalothin between the peak and trough concentrations.

cephacetrile and 17 of cephalothin/cephaloridine. Because all treatment was under blind code, this proportional distribution was expected in each patient category. Analysis showed no significant difference in deaths among patients who received cephradine or cephalothin. The relatively large difference in the number of patients in group II, given a shortened course of therapy, is of borderline statistical significance. Reasons for the premature discontinuation of cephradine were directly related to drug effects in four of nine patients. In the others, treatment was stopped

TABLE 4. Levels and excretion of cephalosporins by patients without azotemia^a

Determination	Avg values $\pm$ SD	
	Cephacetrile (N = 12)	Cephalothin (N = 2)
Urine		
Concn (mg/ml; 6-h period)	2.62 $\pm$ 0.57	0.85 $\pm$ 0.3
Dose excreted (%; 6-h period)	75.3 $\pm$ 11.8	33.9 $\pm$ 4
Plasma		
Mid-point concn (μ g/ml; calculated from peak and trough)	42.5 $\pm$ 9.8	12 $\pm$ 7
Renal clearance (ml/min)	210 $\pm$ 71	241

^a Dose was 2.0 g intravenously every 6 h for 3 to 6 days.

because the etiological organism was resistant or specific infection was not detected. Of the patients who completed therapy, group III, there was a greater number who were switched from an i.v. to an i.m. route of administration of cephradine compared with the cephalothin/cephaloridine regimen; this also is of borderline statistical significance. If these two factors are combined, i.e., a shortened course of therapy for drug-related causes and a switch from i.v. to i.m. treatment, and this number is compared with those completing a full course of i.v. therapy on each regimen, the difference in the distribution of patients between cephradine and cephalothin is significant ($P < 0.01$). This suggests a lower drug tolerability of cephradine by the i.v. route.

TABLE 5. *Treatment regimen of study patients*

Post-treatment category of study patients	Treatment regimen ^a			Total
	Route	Cephacetrile (i.v. and/or i.m.)	Cephalothin (i.v.) and cephaloridine (i.m.)	
I. Deaths	i.v. only	6	2	8
	i.v. and i.m.	1	0	1
II. Shortened treatment	i.v. only	9	0	9
III. Completed treatment	i.v. only	4	8	12
	i.v. and i.m.	7	2	9
	i.m. only	1	1	2
IV. Prophylactic use		3	4	7
		31 Courses (30 Patients)	17 Courses (16 Patients)	48 Courses (46 Patients)

^a The investigational design provided for two of three patients to be treated with cephacetrile by random assignment. All patients except two noted were started with i.v. treatment. A shortened course or switch to i.m. route was the decision of the primary physicians.

The drugs had no apparent contributing role in the cause of death in any of the fatal cases. Only one of nine had a drug-related adverse event, which was superinfection of the urinary tract with *Pseudomonas aeruginosa*. Among the other patients treated, thrombophlebitis was a frequent consequence of i.v. administration of either cephalosporin, occurring in 35% of patients receiving cephacetrile and 27% of those given cephalothin (Table 6). The difference is not statistically significant. Increased platelet counts (sometimes over $10^6/\text{mm}^3$) and reticulocytosis were observed and possibly related to the treatment given. Changes in renal functions, both improvement and deterioration, occurred, but with rare exception they seemed most logically explained by the course of the underlying diseases rather than by a drug effect. Serum enzymes that reflect liver damage occasionally showed modest elevation during treatment; two patients developed a drug-related, positive direct Coombs test.

Superinfection of the urine with resistant organisms of *Pseudomonas*, *Enterobacter*, and *Candida* species occurred in three of seven patients treated with cephacetrile; herellea infection complicated therapy in one of two treated for pneumonia, and herellea and pseudomonas superinfected two of four patients treated for wound infections. Thus, in approximately one-half of patients treated for urinary, respiratory, or wound infections, cephacetrile was complicated by superinfection. This was of more overt consequence than among seven similar patients given cephalothin.

The different reactions recorded in Table 6 tended to occur in different patients; therefore, thrombophlebitis, superinfection, or a positive

TABLE 6. *Unwanted responses associated with cephalosporin therapy*

Determination	Cephacetrile	Cephalothin
No. of courses observed	21 ^a	11 ^a
Thrombophlebitis	8 (1)	3
Positive Coombs test	1	1
Blood alterations		
Reticulocytosis (>3%)	4 (2)	1 (1)
Thrombocytosis (>500,000)	7 [2]	4 [1]
Eosinophilia (>10%)	0	1
Elevation of		
Blood urea nitrogen	1	0
Serum enzymes from liver	6 [4]	1 [1]
Superinfection		
Urine	6 [3]	1
Wound	3 [3]	0
Lung	1	1 [1]
No. of patients		
With one or more adverse responses	17	8
Total	20	10

^a Patients who died (all non-drug related) and those given prophylactic treatment are excluded. The numbers in parentheses and brackets are, respectively, patients in whom the disease state could have caused the response and patients receiving concurrent treatment that could have been a factor.

Coombs test were adverse changes noted in 12 of 20 patients who survived therapy with cephacetrile and 3 of 10 given cephalothin. This is an overall incidence of 48% for these three conditions and not significantly different for the two drug regimens.

DISCUSSION

This investigation was planned to interfere as little as possible with the primary physicians'

prescribing habits in the use of cephalosporin antibiotics and to compare, under these conditions, an investigational new drug with closely related established products. Cephalosporin treatment was prescribed for a broad range of conditions, including prophylaxis, the treatment of simple urinary tract infections, and also severe or life-threatening infections in various body tissues. Both gram-negative and gram-positive bacterial infections were included. Approximately one-third of the time, the specific etiology was not known before treatment was started, and commonly physicians combined cephalosporin with another antibiotic. These practices did not always provide good individual study cases, but the results provide a factual basis for the comparison of drugs regarding the methods of use, acceptability by patients and physicians, complications, and overall effectiveness. The study represents one of the few attempts to obtain controlled comparative information of this type. Although the number of patients in the series is modest, approximately 2,000 laboratory procedures were performed to follow their course and insure recognition or document the absence of toxicity associated with the investigational new drug. These bacteriological, chemical, and serological tests with the clinical observations required exemplify the large expense and effort involved in the attempt to provide an adequate basis to answer simple basic questions of relative efficacy and toxicity between antibiotics for use in man.

In vitro susceptibilities are among the best guidelines to therapy, especially the demonstration of resistance. As might have been predicted from in vitro tests, cephacetrile appeared clinically more active than cephalothin against strains of *Klebsiella* and *Enterobacter*. The finding of a few strains of *Klebsiella* that are highly resistant, almost surely owing to beta-lactamase production, is an ominous sign, because bacteria can transfer the ability to produce such enzymes to other bacteria as an R factor (2, 3). The in vitro effectiveness against *E. coli* and *Proteus mirabilis* was not confirmed in the clinical experience.

The observed average peak serum concentration of cephacetrile is in essential agreement with the observations of Nissenson et al. (9) when adjusted for dose and drug half-life. Hodges et al. (4) reported higher levels with an average serum concentration of 104 $\mu\text{g/ml}$ after 1.5 g of i.v. cephacetrile. It was known that cephalothin produces much lower plasma and urine concentrations of active drug than do other cephalosporins, primarily owing to its conversion to the desacetyl form (5, 6). This

biologically less active metabolite averages about one-third of the dose of cephalothin but can be as high as 90% in some individuals. It is not known whether deacylation of cephalothin is the sole reason for the observed lower blood levels. It is curious that the difference is already observed in specimens taken 1 h after the dose, but the net loss of active drug from plasma between the 1st and 6th hours is proportionately the same (Fig. 2). Thus, whatever the initial mechanism, the process is either discontinuous or not additive with the other modes of plasma clearance beyond the 1st hour. If the volume of distribution of cephalothin were significantly larger, it would be a partial explanation of the lower levels of cephalothin, but data available suggest this is not a major factor (5). The renal clearance of cephacetrile is similar to that of cephalothin, and hepatic excretion of active drug is relatively low (1).

The movement of drug into extravascular tissues and the secretions of various organs, the urine being the most obvious, may be of major importance in the treatment of specific conditions. In relating the pharmacological data to therapeutic results, cephacetrile, which attained higher urine concentrations, was more effective in urinary tract infections, but this trend was not significant. In the case of urinary tract infections, which comprised 41% of this experience, the presence of concentrations (in milligrams per milliliters) of drug in the urine represents a concentration overkill so enormous that major differences in microbial susceptibility and drug pharmacology would be overshadowed.

In addition to in vitro susceptibility and bioavailability of the drug, the influence of the host on the outcome of therapy owing to associated diseases was repeatedly observed by the failure to eradicate susceptible organisms with apparently adequate amounts of antibiotic. Therapy with either regimen was effective to only about 50% of the therapeutic potential. This is disappointing, considering the exclusion of another 15 to 25% of patients with initially resistant strains, but it reflects the severity of the illnesses treated. Use of a simultaneous control group, even though small, provided a basis for the correct evaluation of the new drug within the expected limits of chemotherapy with cephalosporins in such patients.

The controlled experience also permitted the interpretation that there was poorer acceptability of i.v. cephacetrile than cephalothin. The increased frequency of shortened courses and the early switch from i.v. to i.m. therapy are subtle signs that represent minor intolerances.

In view of this and the pharmacological data which show plasma and urine levels of cephacetrile approximately three times greater than those of cephalothin after the same dose without any demonstrated therapeutic benefit, it would seem advantageous to consider use of a lower dose of cephacetrile. Serious gram-negative bacillary infections other than those of the urinary tract would remain as indications for high-dose intravenous administration. However, the limited effect of cephalosporins on *Klebsiella* species, their meager effect on *Enterobacter* bacilli, and the nil effect on organisms of the *Pseudomonas* and *Serratia* genera usually lead physicians to use other antibiotics in the treatment of these common gram-negative infections. Indications for combination therapy in this series were not always clear, but the data represent the practice of the primary physicians, which was to use aminoglycosides with cephalosporins in the treatment of approximately 30% of patients and some other antibiotic in another 20%. The benefit of such combinations over either drug alone against susceptible organisms has not been established.

Although the adverse reactions observed are not life-threatening or serious complications, they cannot be ignored. Thrombocytosis occurred in 11 of 30 patients and 9 of 27 patients reported by Hodges et al. (4), which is more than expected from acute infections (8, 10). Altogether, approximately 75% of patients treated with either of the drugs under study experienced some unwanted reaction. On this basis, and in order to minimize the risk of further transfer of resistance, restricted use of the cephalosporin antibiotics for prophylaxis is recommended.

This limited but controlled experience sug-

gests that cephacetrile can be considered comparable to cephalothin as a therapeutic agent with the possible advantages of higher blood and urine levels and more flexibility in using intramuscular administration, but also perhaps more need to do so.

ACKNOWLEDGMENTS

We thank Paul Miller and his staff for handling and dispensing the coded drugs.

LITERATURE CITED

1. Bogard, J. M., P. Haegele, M. Dorner, and J. Lavillaureix. 1972. Biliary excretion of a new semisynthetic cephalosporin, cephacetrile. *Antimicrob. Ag. Chemother.* 3:19-23.
2. Davies, J. E., and R. Rownd. 1972. Transmissible multiple drug resistance in Enterobacteriaceae. *Science* 176:758-768.
3. Hamilton-Miller, J. M. T., and R. Knox. 1969. Bacterial resistance to penicillins and cephalosporins. *J. Pharm. Pharmacol.* 21:337.
4. Hodges, G. R., J. F. Scholand, and R. L. Perkins. 1973. Cephacetrile: clinical evaluation in 27 patients. *Antimicrob. Ag. Chemother.* 3:228-234.
5. Kirby, W. M. M., J. B. DeMaine, and W. S. Serrill. 1971. Pharmacokinetics of the cephalosporins in healthy volunteers and uremic patients. *Postgrad. Med. J.* 47(Suppl):41-46.
6. Lee, C. C., E. B. Herr, and R. C. Anderson. 1963. Pharmacological and toxicological studies on cephalothin. *Clin. Med.* 70:1123-1138.
7. Litwack, K. 1969. Discussion on chemistry and microbiology of gentamicin. *J. Infect. Dis.* 119:381-382.
8. Marchasin, S., R. D. Wallerstein, and P. M. Aggeler. 1964. Variation of the platelet count in disease. *Calif. Med.* 101:95.
9. Nissenson, A. R., N. W. Levin, and R. H. Parker. 1972. Effect of renal failure and hemodialysis on cephacetrile pharmacokinetics. *Clin. Pharmacol. Therapeut.* 13:887-894.
10. Olef, I. 1936. Differential platelet count. *Arch. Intern. Med.* 57:1163-1185.
11. Sabath, L. D., J. I. Casey, P. A. Ruch, L. L. Stumpf, and M. Finland. 1971. Rapid microassay for circulating nephrotoxic antibiotics. *Antimicrob. Ag. Chemother.* 1970, p. 83-90.