Carbenicillin in the Treatment of Infections Involving Anaerobic Bacteria

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Twenty-one patients with serious infections involving anaerobic bacteria were treated with carbenicillin. Multiple anaerobes were involved in 8 cases, and in 10 cases, facultative anaerobes were also isolated. *Bacteroides fragilis* was isolated in 10 cases. Results were judged excellent in 7 cases, good in 8 cases, and fair in 5 cases. These data suggest that carbenicillin may be an effective antibiotic for the therapy of infections due to anaerobic bacteria, particularly those involving *B. fragilis*.

Anaerobic bacteria are involved in a wide variety of human infections (4, 8, 12, 13). *Bacteroides fragilis*, which plays a prominent role in intra-abdominal and pelvic infections, is frequently resistant to penicillin (6), so the choice of a potentially effective antimicrobial agent for such infections is limited to regimens that include chloramphenicol or clindamycin. However, recent data indicate that carbenicillin is active in vitro against many anaerobic bacteria, including *B. fragilis* (11). Furthermore, it is also active against numerous facultative anaerobes (14). On the basis of these findings, we have been evaluating carbenicillin in the treatment of infections involving anaerobic bacteria. The results obtained with 21 patients seen during the period of December 1972 through December 1974 make up this report.

MATERIALS AND METHODS

Patients. All 21 patients were in patients at Temple University Hospital. Cases were included in the present study only if (i) the patient had received no antibiotic therapy in the previous 7 days or had received antibiotic therapy for 24 h or less prior to inclusion in the study, and (ii) anaerobic bacteria were the only or predominant organisms isolated from a specimen collected prior to or within 24 h of the institution of antimicrobial therapy. Patients with known allergic or toxic reactions to carbenicillin, other penicillins, or cephalosporins were excluded from the study. Since penicillin is clearly effective in anaerobic pleuropulmonary infections (1, 15), patients with such infections were also excluded from the study.

Isolation and identification of bacteria. In most instances, specimens were collected by aspiration from a closed cavity using an 18-gauge needle and syringe. Exceptions to this were (i) endometrial cultures, which were obtained transcervically; (ii) biopsy specimens; and (iii) some wound infections in

which pus was merely aspirated from the open wound. All material collected by needle and syringe were immediately injected into an oxygen-free, medium-free, rubber-stoppered glass tube for transportation to the laboratory. Biopsy specimens were placed in sterile tubes without media and taken immediately to the laboratory. In the laboratory, specimens were passed into an anaerobic chamber where all subsequent manipulations were carried out (9). Anaerobic bacteria were identified by colonial morphology, reaction to Gram stain, growth on selective media, biochemical reactions, and gas-liquid chromatography of fermentation products. The criteria used were those outlined by the Anaerobe Laboratory at Virginia Polytechnic Institute (5). Facultatively anaerobic bacteria were isolated and identified by means of standard techniques (7).

Susceptibility tests. Anaerobic bacteria were tested using the following agar-dilution procedure. After each organism had been isolated and checked for purity, it was inoculated onto prereduced brain heart infusion agar supplemented with yeast extract (0.5%), hemin (0.005%), and vitamin K (0.1 µg/ml) and incubated at 37°C until visible turbidity developed. The agar medium consisted of brain heart infusion base (BBL) with 1.5% agar enriched with 5% laked sheep blood and vitamin K (10 µg/ml). On the day of testing, plates were prepared containing serial dilutions of carbenicillin. The final concentrations of the antibiotic ranged from 0.125 to 256.0 µg/ml. After drying in an incubator for 60 min, the plates were transferred to the anaerobic chamber 4 h before inoculating.

The inoculum was diluted 1:100, and the plates were inoculated in the chamber with approximately 10⁴ colony-forming units with a Steers replicator (10). Plates were incubated for 48 h at 37°C in the anaerobic chamber. All plates were run in duplicate with the appropriate growth controls included. The minimum inhibitory concentration was considered to be the lowest concentration of antibiotic at which no visible growth occurred. Antibiotic susceptibilities for facultative anaerobes were performed by the Kirby-Bauer disk diffusion technique (2).

Therapeutic regimen and evaluation of response.

All patients were initially treated with intravenously given carbenicillin in doses of 300 to 450 mg/kg per 24 h. Duration of therapy ranged from 5 to 22 days. Since intra-abdominal and pelvic infections occasionally involve *Klebsiella* species likely to be resistant to carbenicillin, 14 patients were also given kanamycin, 7.5 mg/kg intramuscularly every 12 h, or gentamicin, 1 to 1.6 mg/kg intramuscularly every 8 h. If all facultatively anaerobic bacteria isolated were susceptible to carbenicillin, treatment with the aminoglycoside antibiotic was discontinued. Only 3 of the 14 patients required continuation of treatment with the aminoglycoside antibiotic for more than 4 days. In addition to antibiotic therapy, 15 patients required some form of surgical drainage. Patients were followed-up for 1 to 11 months after discontinuation of therapy. None had recurrent infections during this time.

Results of therapy were judged according to the following criteria: (i) excellent: clinical resolution or marked improvement and negative cultures or no further drainage from infection site with 4 days; (ii) good: a similar clinical and bacteriological response within 7 days; (iii) fair: ultimate clinical and bacteriological response without changing or adding antibiotics; and (iv) poor: failure to response or relapse necessitating a change in antibiotics.

RESULTS

Types of infections. The kinds of infections treated are listed in Table 1. These included peritonitis (five), hepatic abscess (two), endomyometritis (four), salpingitis (four), superficial cellulitis in the extremities of narcotic addicts, (four), and wound infections (two). Multiple anaerobes were isolated in nine cases, and anaerobic bacteria were the only isolates in nine cases. *B. fragilis* was isolated in 10 cases.

Bacteriology. The identification and the sources of the bacteria isolated are presented in Table 2. *Bacteroides* species accounted for 16 of the 31 anaerobic bacteria isolated, with *B. fragilis* the most common anaerobe isolated. *Escherichia coli* and *Streptococcus* species were the most common facultative anaerobes isolated.

Antibiotic susceptibilities. Thirty of 31 anaerobic bacteria isolated were inhibited by 64 µg or less of carbenicillin per ml. The one resistant anaerobe, a strain of *B. fragilis*, was inhibited by 256 µg/ml. The *Klebsiella pneumoniae* strain, the *Enterobacter* species, and one of the *Proteus* species isolated were resistant to carbenicillin.

Clinical response. The responses of the patients to carbenicillin therapy are shown in Table 3. The response was judged excellent in seven cases, good in eight, fair in five, and poor in one. In four of the five cases with a fair response, the patient ultimately developed a localized abscess requiring surgical drainage.

TABLE 1. Infections treated with carbenicillin

Site	No.	Multiple anaerobes	Anaerobes only	<i>Bacteroides fragilis</i>
Peritonitis	5	3		5
Hepatic abscess	2	2	1	
Endomyometritis	4	1	3	2
Salpingitis	4	1	3	2
Cellulitis	4	2	2	
Wound infection	2			1

TABLE 2. Bacteria isolated

Anaerobic bacteria	No.	Facultative anaerobes	No.
<i>Bacteroides fragilis</i>	10	<i>Escherichia coli</i>	7
<i>B. melaninogenicus</i>	4	<i>Klebsiella pneumoniae</i>	1
<i>Bacteroides</i> spp.	2	<i>Enterobacter</i> spp.	1
<i>Fusobacterium</i> spp.	4	<i>Proteus</i> spp.	2
<i>Peptostreptococcus</i> spp.	6	<i>Streptococcus</i> spp.	6
<i>Peptococcus</i> spp.	3		
<i>Clostridium</i> spp.	3		

TABLE 3. Response to therapy

Infection	No. of cases	Response			
		Excellent	Good	Fair	Poor
Peritonitis	5		3	1	1
Hepatic abscess	2		1	1	
Endomyometritis	4	2	1	1	
Salpingitis	4	2	2		
Cellulitis	4	2	1	1	
Wound infection	2	1		1	

The poor response was in a patient with generalized peritonitis. Multiple anaerobes were isolated from the peritoneal cavity and *B. fragilis* was isolated from an initial blood culture. All of these anaerobes were susceptible to carbenicillin. The patient developed shock, disseminated intravascular coagulation, and expired after 4 days of therapy. In one case of cellulitis of the leg in a narcotic addict, multiple anaerobes, including a carbenicillin-resistant *B. fragilis*, were isolated. Despite the presence of the resistant *B. fragilis*, there was a good response to carbenicillin therapy.

Table 4 summarizes the results in those cases in which *B. fragilis* was isolated. Response to carbenicillin therapy was considered excellent in four, good in four, fair in one, and poor in one.

Tolerance and toxicity. Carbenicillin was generally well tolerated by the majority of pa-

TABLE 4. Response to therapy in cases in which *Bacterioides fragilis* was isolated

Infection	No. of cases	Response			
		Excellent	Good	Fair	Poor
Peritonitis	5		3	1	1
Endomyometritis	2	2			
Salpingitis	2	1	1		
Wound infection	1	1			

tients. Six patients developed abnormalities of hepatic enzymes, but in no case could this definitely be attributed to carbenicillin. Three patients, also concomitantly receiving an aminoglycoside antibiotic, developed transient increases in blood urea nitrogen and serum creatinine levels. Finally, one patient developed a maculopapular rash attributed to carbenicillin.

DISCUSSION

The results of in vitro susceptibility tests on isolates from the 21 cases reported here lend further support to the previous observation that the majority of anaerobic bacteria, including *B. fragilis*, are susceptible to carbenicillin. The therapeutic response in these cases suggest that carbenicillin may be an effective agent in the therapy of infections involving anaerobic bacteria suspected or known to be *B. fragilis*. However, some caution must be exercised in evaluating these results, since surgical drainage procedures were an integral and important part of the therapy in many of these cases. Despite problems such as these, we believe that carbenicillin warrants further evaluation in the therapy of intra-abdominal and pelvic infections suspected or known to involve *B. fragilis*. Such studies should be undertaken with caution since a small percentage of strains of *B. fragilis* may be resistant to carbenicillin (11). In addition, continuous surveillance of the susceptibility of anaerobes isolated must be maintained, since it is not yet known whether development of resistance to carbenicillin will be a problem. These results should be considered together with the cost and relative toxicity of

carbenicillin to define the precise role of this agent in the therapy of anaerobic infections.

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