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Therapy of Obstetrical Infections with Moxalactam

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We evaluated moxalactam in 62 patients with puerperal or postabortal genital infections. In all patients, the initial dose was 6 g/day. In 84% of patients, we found anaerobes in genital specimens. Of aerobic isolates, only enterococci were resistant. Among anaerobes tested, only two isolates (a *Clostridium leptum* and a *Bacteroides disiens*) had minimal inhibitory concentrations of ≥32 μg/ml. Good clinical responses occurred in 56 of 62 (90%). Moxalactam was well tolerated with little local irritation and minimal hepatic, renal, or hematological abnormalities.

A new β-lactam antibiotic, moxalactam (formerly known as LY127935), possesses an unusually broad in vitro spectrum of activity, including *Bacteroides fragilis* and many gram-negative aerobes (1, 3). Though other agents are more active against gram-positive cocci, nearly all of these organisms are susceptible to readily achievable levels of this new antibiotic (1). Since female genital infections involve a broad variety of aerobic and anaerobic microorganisms, we evaluated the efficacy and safety of moxalactam in treating a number of these infections.

MATERIALS AND METHODS

Patients. We invited participation of patients who had puerperal or postabortal infection on the obstetric-gynecologic service of the Bexar County Teaching Hospitals. In a prospective evaluation, we have found that 38.5% of patients having cesarean sections developed intrauterine infection (5). After vaginal delivery, we estimate that intrauterine infection develops in 2 to 3%. Minimal criteria were fever ≥38.4°C, uterine tenderness, and leukocytosis. After obtaining written, informed consent, we obtained specimens for culture from the peripheral blood and from the uterine cavity by a lavage technique (6). The initial dose of moxalactam was 2 g intravenously every 8 h. Before, during, and after therapy, we performed the following studies: urinalysis, complete blood count, blood urea nitrogen, serum creatinine, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, serum alkaline phosphatase, and total bilirubin.

Bacteriological studies. We plated uterine specimens directly, or if collected at night, injected them into a Port-A-Cul vial (BBL Microbiology Systems, Cockeysville, Md.). We employed common media for isolation of aerobes and anaerobes and used biochemical systems (Minitek Enteric and Minitek Anaerobe, BBL Microbiology Systems) and gas-liquid chromatography for identification (7). For susceptibility testing of gram-negative aerobic rods, we used the standard Kirby-Bauer method with a 30-mg disk. We considered organisms susceptible if the zone of inhibition was greater than 18 mm. For minimal inhibitory concentrations (MICs) of anaerobes and selected gram-positive aerobic cocci, we employed an agar dilution method (11). The hospital laboratory performed the blood and urine cultures with standard techniques.

Clinical response. We judged the response to therapy as successful when there was resolution of signs and symptoms of infection within 3 days without recurrence. We considered the course of therapy to be failure when there were persistent or unresolving signs for more than 3 days and when other antibiotic therapy was used. If common surgical drainage procedures (such as wound drainage or dilitation and curettage) were performed, we also considered the initial therapy successful, provided no additional antibiotics were required.

In successful courses, we usually administered moxalactam for a minimum of 5 days. When the response was prompt, we often administered the last day of therapy intramuscularly, 500 mg every 8 h. When a clinical failure occurred, we modified therapy according to clinical judgments and culture results.

We determined the fever index (base 37.22°C or 99°F) for all patients (8).

RESULTS

During the 5-month study interval (August through December, 1979), we evaluated 62 patients. Most (57) had endomyometritis after cesarean section, and three had endomyometritis after vaginal delivery. Two others had postabortal infection. These infections generally developed on days 2 to 4 after delivery. No patients had received prophylactic antibiotics, and only one had received prior antibiotic therapy (as an outpatient). The mean oral temperature at diagnosis was 38.6°C, and the mean white blood cell count was 14,200/mm^3.

From the 62 patients, there was a total of 201 genital isolates (Table 1). In 52 of 62 patients (84%), we found anaerobes in the uterine culture. None of the 30 aerobic gram-negative rods tested was resistant, with all having inhibitory zones >18 mm in diameter. The isolate of *Yersinia*

TABLE 1. *Genital tract isolates from 62 patients treated with moxalactam*

Species	No.
Group B streptococci	10
Enterococci	6
Streptococcus pneumoniae	1
Staphylococcus aureus	1
Alpha streptococci	3
Lactobacilli	31
Diphtheroids	13
Staphylococcus epidermidis	14
Other aerobic gram-positive organisms	5
Escherichia coli	20
Klebsiella pneumoniae	4
Proteus mirabilis	3
Enterobacter hafniae	1
Enterobacter cloacae	1
Citrobacter diversus	1
Yersinia sp.	1
Candida sp.	4
Total aerobes	119
Peptococcus prevotii	5
Peptococcus asaccharolyticus	1
Other anaerobic gram-positive cocci	1
Propionibacterium sp.	7
Clostridium sp.	13
Eubacterium lentum	15
Fusobacterium mortiferum	4
Fusobacterium necrophorum	4
Bacteroides isolates[a]	32
Total anaerobes	82

[a] The species of these 32 isolates are presented in Table 2.

species was not tested. In Table 2, we present the MICs of anaerobic and selected aerobic organisms. Among the anaerobes, only two isolates (one *Clostridium leptum* and one *Bacteroides disiens*) had MICs of ≥32 μg/ml, and among the aerobes tested, only five enterococcal isolates were resistant. These seven resistant isolates were identified in cultures of patients with good clinical responses.

Since most of these infections were diagnosed at night, the vast majority of specimens (55 of 62) were injected into the transport vials. The results were generally the same for specimens plated directly and those plated after transport.

Four patients (6%) had bacteremia, with the following organisms: group B streptococci, *Escherichia coli*, *Staphylococcus aureus*, and peptostreptococci (1 each).

Good clinical responses occurred in 56 of 62 patients (90%). In these patients, therapy ranged from 4 to 17 days, with a mean of 6.9 days. In five of these patients, adjunctive surgical drainage was carried out (wound drainage, 4; curettage, 1).

The six patients with poor clinical responses all had endomyometritis after cesarean section. In three, we identified possible causes of persistent fever as: wound abscess and possible septic pelvic thrombophlebitis (1), wound seroma (1), and marked phlebitis from an intravenous catheter (1). In the remaining three, there was no apparent cause for the failure. Additional therapy was effective in these six patients and consisted of other antibiotics (clindamycin and gentamicin, 6; wound drainage, 2; intravenous heparin, 1; and local therapy for phlebitis, 1).

In one other patient, there was a good response of fever and uterine tenderness by day 4 of therapy, but a marked paralytic ileus persisted. On day 6, the patient's wound eviscerated. After wound repair, her recovery was uneventful, and she remained afebrile on moxalactam therapy. Because of an error in the protocol, the patient received one dose each of clindamycin and gentamicin immediately before wound repair.

The mean fever index for the 56 patients with good clinical responses was 53 degree F-hours (29 degree C-hours), whereas for the 6 patients with poor responses, it was 113 degree F-hours (62 degree C-hours).

Patients tolerated moxalactam very well. There were no complaints of irritation upon intravenous injection, and 6 of 52 receiving intramuscular injections of the drug experienced mild, transient (<20 min) burning. Though two

TABLE 2. *MIC of moxalactam for selected organisms tested*

Species (no. of isolates tested)	MIC (μg/ml)	
	MIC_{50}	Range
Group B streptococci (2)[a]	4	4
Enterococci (6)	>128	4->128
Bacteroides fragilis group[b] (2)	1	0.5–1.0
Bacteroides melaninogenicus[c] (6)	2	0.25–4
Bacteroides bivius (12)	2	0.25–4
Bacteroides disiens (8)	1	0.25–64
Bacteroides sp. (4)	4	2–8
Fusobacterium sp. (8)	0.25	0.25–2
Eubacterium lentum (16)	0.25	0.25
Propionibacterium sp. (7)	2	0.25–4
Peptococci-peptostreptococci (6)[a]	0.25	0.25–1
Clostridium sp. (13)	2	0.25–128

[a] Not all isolates were available for testing.

[b] This group includes *Bacteroides fragilis*, *Bacteroides distasonsi*, *Bacteroides thetaiotaomicron*, and *Bacteroides vulgatus*.

[c] This includes *Bacteroides asaccharolyticus*.

patients had catheter-associated phlebitis, neither episode was located in a site used for moxalactam administration. Three patients had minimal elevations (less than 10 U) of serum glutamic oxalacetic transaminase or serum glutamic pyruvic transaminase, but none had abnormalities of other liver function tests, blood urea nitrogen, creatinine, or blood count related to moxalactam.

DISCUSSION

There is little agreement on the initial treatment of most obstetric-gynecological infections among inpatients. In view of the polymicrobial nature of these infections, most patients receive broad-spectrum therapy, often with a combination of agents. We evaluated moxalactam as single-agent therapy for patients with obstetrical infections, in view of its unusually broad in vitro activity.

Most of the patients were mildly to moderately ill, with only 6% having documented bacteremia. By these characteristics, the patients are typical of most patients with puerperal infection (12). A total of 90% of the patients (89% of those with cesarean section) had good clinical responses. In the six clinical failures, we identified possible causes of antibiotic failure in three. In previous studies of this type of infection, we have found causes of failure for other antibiotics in a similar percentage (4, 5). In the few failures in the present trial, local factors seemed important, but we did not isolate any resistant organisms. Indeed, we did not find a close correlation between MICs and clinical response. However, most of the resistant organisms (five of seven) were enterococci, well known as organisms usually of low virulence. As with most clinical trials, a degree of discordance between sensitivity patterns and clinical response is not surprising.

One of the problems in evaluating antibiotic therapy in puerperal and postabortal infections is the difficulty in obtaining a satisfactory genital tract specimen for culture. Vaginal and endocervical swabs provide mediocre specimens as lower genital tract organisms are probably not identical to organisms in the uterus. Though a new double-lumen-protected swab is being evaluated (10), this technique has not been generally available. Further, since these results have not been compared with those of blood, cul-de-sac, or transabdominal specimens, the advantages of this technique must be presently considered as presumptive. Thus, we have employed a lavage technique. Though it does not completely avoid the problem of contamination, the technique does sample a large portion of the endometrium and has been safe and simple.

Moxalactam was well tolerated, with no irritation upon intravenous injection and with few instances of pain after intramuscular injection. We observed only minimal adverse hepatic, renal, or hematological reactions related to drug use.

In evaluation of other new, cephalosporin-like agents for therapy of similar infections, most investigators have found a high degree of cure. In the same institution, we reported that cefamandole was effective in 50 of 60 (83%) patients with endometritis after cesarean section (4). In the analysis of response by fever index, we found that patients responding to cefamandole had a mean fever index of 80 degree F-hours (44 degree C-hours). For patients with a poor response, it was 150 degree F-hours (82.5 degree C-hours) (4). Though the mean fever index was lower for patients treated with moxalactam (both for cures and failures), this difference does not necessarily indicate a superior response as fever index is also influenced by severity of the infection, fever before therapy, and use of antipyretics. Further, there is no agreement regarding definition of a clinically meaningful difference in fever indices.

Studying a variety of obstetric-gynecological infections, Cunningham and colleagues found that 90% responded to cefamandole alone (2). Sweet and Ledger (13) and Ledger and Smith (9) found that cefoxitin was curative in 92 and 94% of female patients with genital infections. Thus, the efficacy of moxalactam in this small initial study compared favorably with these other new agents. However, these studies included patients with infections of varying severity, and comparative studies may reveal whether the unusually broad spectrum of moxalactam is accompanied by a greater clinical efficacy.

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