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Moxalactam Treatment of Anaerobic Infections in Cancer Patients

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Of 30 patients with predominantly anaerobic localized infections superimposed on chronic tissue damage related to trauma, ischemia, or tumor, 22 (73%) responded satisfactorily to moxalactam therapy. Moxalactam-resistant anaerobic pathogens emerged in two patients and were responsible for treatment failure. In six patients, two of whom also acquired resistant anaerobic pathogens, isolation of moxalactam-resistant aerobic pathogens increased during therapy.

Moxalactam is a new broad-spectrum cephalosporin with remarkable activity against *Enterobacteriaceae*. It is also effective in vitro against *Pseudomonas aeruginosa* and anaerobic microorganisms, including *Bacteroides* spp. However, clinical experience with moxalactam in infections caused by these latter microorganisms is still limited.

For this reason, we investigated the efficacy of moxalactam in patients with localized infections caused by anaerobic microorganisms, most frequently superimposed on malignant tumors. The choice of a broad-spectrum therapy, potentially active against aerobic and anaerobic microorganisms which are often associated within the site of the infection, appeared to be a logical approach to these complicated mixed infections. However, the respective roles of aerobic and anaerobic microorganisms under these circumstances are still not clearly defined.

MATERIALS AND METHODS

Thirty patients with microbiologically demonstrated anaerobic or anaerobic-aerobic localized infections were studied. All patients were hospitalized at the Institut Jules Bordet and exhibited a similar degree of debility. The group included 19 males and 11 females with a mean age of 54.5 years (range, 21 to 77). Of these patients, 23 had an underlying neoplastic disease. In 10 patients, infection was directly associated with a primary tumor producing a complex clinical situation of a mixed anaerobic-aerobic infection superimposed on a tumor. In the other patients, anaerobic infections were associated with abscesses (eight patients) or infections of the upper (six patients) or lower (6 patients) respiratory tract. The infections of the upper respiratory tract were usually associated with tracheostomy or prolonged tracheal intubation.

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Patients received moxalactam intravenously at the onset of the infection. A dose of 2 g was dissolved in 50 ml of 5% glucose in water and infused over a 15-min period every 8 h. After 72 h, if the clinical condition of the patient was improving, the dose of moxalactam was reduced to 2 g every 12 h and was occasionally given intramuscularly. No other antibiotics were administered concomitantly. Clinical responses were considered favorable when the initial clinical signs and symptoms related to the infection disappeared during therapy or improved markedly. Bacteriological cure was not considered necessary for a favorable clinical response. Intolerance to the antibiotic, not requiring its discontinuation, and asymptomatic colonization of the site of the infection were considered to be compatible with a favorable clinical response.

Aerobic and anaerobic cultures were obtained from the site of infection and from the blood of all patients before and during therapy. In most patients, these cultures were repeated after discontinuation of the antibiotic.

The anaerobic microorganisms were identified by the method of Labbe (5). Anaerobic conditions for cultures were provided by using the GasPak system (BBL Microbiology Systems). No anaerobic cabinet was used for the plating of clinical specimens or for the manipulations required by subculturing. In most cases, however, the clinical specimens were plated within a few minutes after collection. No special precautions were taken for specimen transport. Routine techniques were used for isolation and identification of aerobic microorganisms.

The minimal inhibitory concentrations (MICs) were determined by a broth dilution method, using peptone-yeast extract-glucose. Antibiotic concentrations ranged from 0.03 to 50 μg/ml. A volume of a broth dilution of an overnight culture was added to each tube so that the final inoculum was 10^6 organisms per ml. Tubes were incubated for 48 h under anaerobic conditions at 37°C and then examined for evidence of growth. Anaerobic and aerobic pathogens were considered to be resistant in vitro to moxalactam if the MIC was higher than 25 μg/ml and fully susceptible to moxalactam if the MIC was less than or equal to 3 μg/ml.

Hematological examination and determination of blood urea, creatinine, alkaline phosphatase, bilirubin, and transaminases were performed before, during and after therapy.

RESULTS

The clinical signs and symptoms in most patients were those of a focal infection superimposed on some kind of localized tissue damage. Most infectious sites were necrotic and purulent. Before treatment, a foul smell was observed at the site of infection in all cases. The disappearance of the foul smell and relief of pain at the site of infection were usually the first indications of a favorable response to moxalactam therapy. Fevers higher than 38.5°C were observed in 12 of 30 patients, and elevated leucocyte counts were present in 14 of 30 cases. Neutropenia, as a consequence of cytostatic therapy, was present in four patients. Most patients complained of discomfort, pain, or both at the site of infection.

There were 83 anaerobic isolates in the 30 patients (2.7 pathogens per patient) (Table 1). Of these isolates, 46 (55%) were fully susceptible to moxalactam and 6 (7%) were resistant (MIC >25 μg/ml). Thirty isolates could not be tested for susceptibility. Aerobic pathogens were associated with the anaerobic microorganisms in 16 (53%) of 30 infections. Gram-negative bacilli were present in 11 infections (37%), staphylococci in 4 infections (13%), and a *Streptococcus* sp. in 1 infection. In 4 of 11 patients, there was a mixed infection with gram-negative bacilli and enterococci.

Of the anaerobic isolates, 6 were resistant to moxalactam with MICs greater than 25 μg/ml. Included were two *Bacteroides ovatus* isolates, one *Bacteroides thetaiotaomicron*, one *Peptostreptococcus productus*, one *Streptococcus intermedius*, and one *Veilonella parvula*. In addition, one *Bacteroides fragilis* isolate and one *Bacteroides bivius* had an MIC greater than 3 but lower than 25 μg of moxalactam per ml. One infection was caused by two resistant anaerobic pathogens and one of intermediate susceptibility, and one infection was caused by two resistant anaerobic pathogens.

In four of five treatment failures, there were persisting or emerging gram-negative bacilli. In three of these four cases, the gram-negative pathogen was a *Pseudomonas aeruginosa* strain (two strains were resistant to moxalactam, and one was not tested).

Group D streptococci (and *Enterobacteriaceae*) were isolated from four patients before treatment, but were not recovered during therapy in three of the patients. Despite a favorable outcome, colonization persisted in the fourth patient. Three other patients acquired group D streptococci during treatment. One of these patients was also superinfected with resistant aerobic and anaerobic pathogens. Two others initially had no associated aerobes. Overall 7 of 30 patients (23%) underwent colonization by group D streptococci. Two patients had simultaneously emerging aerobic and anaerobic resistant pathogens; neither patient responded to moxalactam.

A favorable outcome was seen in 22 of 30 patients (73%). The rate of success was similar in patients with strictly anaerobic infections and in those with mixed anaerobic-aerobic infections. Five patients (17%) failed to respond to moxalactam. In three of the patients, failure to respond to moxalactam therapy was probably related to insufficient drainage of a purulent collection at the site of infection (patients 14, 16, and 27). Two other patients (patients 19 and 22) failed to repond to moxalactam therapy, but insufficient drainage of infection probably did not play a major role in that outcome. There were three (10%) recurrent infections (patients 2, 22, and 26). There were four infections caused predominantly by anaerobic organisms resistant to moxalactam, only one of which failed to respond to therapy. Emergence of moxalactam-resistant anaerobic microorganisms were observed in two infections which failed to respond to therapy. Moxalactam-resistant aerobic pathogens appeared during the therapy of six patients; in three patients, this event was responsible for further infection and played a role in the unfavorable outcome

Overall, moxalactam therapy was extremely well tolerated. Reversible side effects of moxalactam, not severe enough to require discontinuation of therapy, included a skin rash in one patient, diarrhea in one patient, and elevation of the alkaline phosphatase in two patients. In another patient who exhibited elevations of alkaline phosphatase, γ-glutamyltransferase, and bilirubin, moxalactam was discontinued, and all of the abnormal values returned to the normal within 3 weeks. It is difficult to evaluate minor side effects in patients who have a severe underlying disease which in itself might have accounted for some of the observed changes.

DISCUSSION

Localized infections superimposed on tumors or other chronic tissue damage, although not often associated with bacteremia (2, 7), represent an interesting model for the understanding of anaerobic infections. Despite the frequent presence of aerobic microorganisms and anaerobic pathogens, these infections respond as well to specific antianaerobic therapy (clindamycin or tinidazole) as to a treatment which is active against both anaerobic and aerobic pathogens

TABLE 1. Clinical and bacteriological data of 30 patients treated with moxalactam

Patient no.	Sex	Age	Anaerobic infection			Pathogens and susceptibility to moxalactam[a]	Pathogens isolated at end of therapy	Surgical drainage	Clinical outcome
			Underlying disease	Site	Diagnostic procedure				
1	F	68	Anal tumor	Ulcerated tumor cellulitis	Swab	*Bacteroides fragilis* (S), *Bacteroides melaninogenicus* (S), *Proteus morganii* (S), *Streptococcus* group D (R)	Eradication	No	Success
2	M	76	Laryngeal tumor	Ulcerated tumor, laryngostomy	Laryngostomy aspiration	*Bacteroides melaninogenicus*, *Streptococcus* alpha-hemolytic	Persistence of *Bacteroides melaninogenicus*	No	Recurrence
3	F	57	None	Breast abscess	Puncture	*Propionibacterium* sp. (S), *Peptococcus* sp. (S), no aerobes	Eradication	Yes	Success
4	M	69	Tracheal tumor	Tracheostomy	Tracheostomy aspiration, swab	*Bacteroides melaninogenicus*, *Fusobacterium* sp., *Streptococcus* alpha-hemolytic	Eradication	No	Success
5	F	56	Cervix tumor	Pelvic abscess	Surgical exploration	*Bacteroides fragilis* (S), *Peptococcus asacharolyticus* (S), no aerobes	Eradication	Yes	Success
6	M	56	Oropharynx	Tracheostomy	Tracheostomy aspiration	*Fusobacterium*, *Bacteroides melaninogenicus*, *Streptococcus* alpha-hemolytic	Eradication	No	Success
7	F	66	Anal tumor	Abdominal wound infection	Puncture	*Bacteroides fragilis* (S), *Bifidobacterium* sp., (S), *Eubacterium* sp. (S), *Escherichia coli* (S), *Streptococcus* group D (R)	Eradication Eradication	Yes	Success

8	F	48	Oropharynx tumor	Ulcerated tumor	Swab	*Fusobacterium* sp., *Bacteroides melaninogenicus*, *Streptococcus* alpha-hemolytic	Emergence and colonization by *Streptococcus* group D (R)	No	Success
9	M	33	Hodgkin's disease	Cervical wound infection	Aspiration	*Peptococcus asacharolyticus* (S), no aerobes	Eradication	Yes	Success
10	M	21	Multiple trauma, coma intubation	Bronchopneumonia	Tracheostomy aspiration	*Bacteroides vulgatus* (S), *Staphylococcus aureus* (S)	*Bacteroides melaninogenicus*	No	Success
11	M	44	Oropharynx tumor	Ear and nose ulcerated tumor	Swab	*Bacteroides melaninogenicus* (S), *Bacteroides bivius* (S), *Pseudomonas aeruginosa*, *Streptococcus* group D (R)	*Pseudomonas aeruginosa*	No	Success
12	M	72	Colon tumor	Abdominal wall abscess	Puncture	*Bacteroides fragilis*, *Bacteroides ovatus*, *Streptococcus intermedius*, *Escherichia coli*, *Proteus mirabilis*	*Bacteroides ovatus*, *Bacteroides fragilis*	Yes	Success
13	M	51	Neck tumor	Tracheostomy	Tracheostomy aspiration	*Bacteroides fragilis*, *Bacteroides bivius*, *Streptococcus* alpha-hemolytic	*Streptococcus* alpha-hemolytic	No	Success
14	M	77	Colon cancer, coma	Otitis media, cerebral abscess, ventriculitis	Surgical exploration	*Bacteroides thetaiotaomicron* (R), *Bacteroides fragilis* (S), *Peptostreptococcus* (S), no aerobes	Eradication	Yes	Failure, died before end of therapy
15	F	26	Acute leukemia, neutropenia	Dental abscess	Puncture	*Bacteroides oralis* (S), *Bacteroides fragilis* (S), *Neisseria* sp.	Eradication	Spontaneous drainage	Success

TABLE 1—*Continued*

Patient no.	Sex	Age	Anaerobic infection			Pathogens and susceptibility to moxalactam[a]	Pathogens isolated at end of therapy	Surgical drainage	Clinical outcome
			Underlying disease	Site	Diagnostic procedure				
16	F	38	Head trauma, coma	Sinusitis	Aspiration	*Bacteroides nonfragilis* (S), *Fusobacterium* sp., *Bacteroides melaninogenicus*, *Pseudomonas aeruginosa* (R), *Escherichia coli* (S)	*Fusobacterium* sp., *Bacteroides melaninogenicus* *Pseudomonas aeruginosa* (R)	No	Failure, required anti-*Pseudomonas* therapy
17	F	51	Cervix tumor	Ulcerated tumor	Vaginal swab	*Bacteroides ovatus* (R), *Veilonella parvula* (R), *Bacteroides fragilis* (S), no aerobes	*Streptococcus* group D (R)	No	Success, *Streptococcus* group D colonization
18	M	60	Lung tumor	Pneumonia	Transtracheal aspiration	*Bacteroides bivius* (S), *Peptostreptococcus* sp. (S), *Klebsiella pneumoniae*, *Escherichia coli* (S)	Eradication	No	Success
19	M	66	Acute leukemia, neutropenia	Toe cellulitis	Puncture	*Peptococcus* sp. (S), *Proteus mirabilis* (S)	*Bacteroides fragilis* (R), *Clostridium* sp. (R), *Streptococcus* group D (R)	No	Failure
20	F	58	Esophagus tumor	Pulmonary abscess, pleurisy	Lung puncture	*Peptococcus* sp. (R), *Bifidobacterium* sp. (S), *Klebsiella pneumoniae*	Eradication	Yes	Success
21	M	50	Esophagus tumor	Pneumonia	Transtracheal aspiration	*Peptostreptococcus productus* (R), *Bacteroides bivius* (S), no aerobes	Eradication	No	Success
22	M	42	Subdural hematoma, epilepsy	Pneumonia	Transtracheal aspiration	*Bacteroides bivius* (S), *Fusobacterium nucleatum* (S), *Staphylococcus aureus* (R)	*Fusobacterium nucleatum*	No	Recurrence

23	M	53	Lung tumor	Mediastinal abscess	Sputum	*Bacteroides bivius*, *Bacteroides melaninogenicus*, *Klebsiella pneumoniae*	*Bacteroides melaninogenicus*, *Pseudomonas aeruginosa*	No	Failure, died of hemoptysis before end of therapy
24	M	42	Subdural hematoma, epilepsy	Pneumonia	Sputum	*Bacteroides bivius* (S), *Fusobacterium nucleatum* (S), no aerobes	*Staphylococcus aureus*	No	Success
25	F	49	Breast cancer	Chest wall cellulitis and ulceration	Aspiration	*Peptostreptococcus intermedius* (I), *Peptostreptococcus prevotii* (S), *Staphylococcus aureus*	Eradication	No	Success, cutaneous rash
26	M	69	Tumor maxilla	Ulcerated tumor	Swab	*Bacteroides melaninogenicus*, *Staphylococcus aureus* (I)	Eradication	No	Recurrence, moxalactam therapy ended because of cholostatic hepatitis, clindamycin successfully used later
27	F	67	Brain stem hemorrhage, hypertension intubated	Tracheostomy wound	Wound aspiration	*Bacteroides bivius* (S), *Fusobacterium nucleatum* (S), no aerobes	*Bacteroides bivius* (R), *Pseudomonas aeruginosa* (R)	No	Failure
28	M	77	Ear tumor	Ulcerated tumor	Swab	*Bacteroides bivius* (S), *Streptococcus* group G (I)	Eradication	No	Success
29	M	58	Mouth tumor	Ulcerated tumor, cellulitis	Swab	*Bacteroides bivius* (S), *Bifidolobacterium* sp. (S), *Escherichia coli* (S), *Streptococcus* group D (R)	*Streptococcus* group D (R)	No	Success
30	M	37	Cerebral contusion, coma tracheostomy	Tracheostomy wound	Wound aspiration	*Bacteroides* spp. (I), *Peptococcus* sp., *Pseudomonas aeruginosa* (R)	Eradication	No	Success, diarrhea

[a] Susceptibility to moxalactam: S, sensitive; R, resistant; and I, intermediate. Not available when not stated.

(cefoxitin or doxycycline) (3, 4). These observations suggest that aerobic pathogens in these complicated localized infections with anaerobes, do not play a major role. In this study, infections caused predominantly by anaerobic pathogens responded as often (73%) as infections caused by mixed anaerobic and aerobic microorganisms. It might be questioned, therefore, whether antimicrobial coverage against both aerobic and anaerobic pathogens is really needed for treatment of such infections. In this series, 22 (73%) of 30 patients with predominantly localized anaerobic infections responded satisfactorily to moxalactam therapy. This rate of response compares favorably with that observed in similar infections with clindamycin or cefoxitin alone (3).

In this study, four infections were caused predominantly by moxalactam-resistant anaerobic pathogens; only one of these failed to respond to moxalactam therapy. In a previous review of our experience with the type of infection studied here, we found that 60% of infections caused by resistant anaerobic pathogens responded to therapy with antimicrobial agents to which the pathogens were resistant in vitro (6). This might suggest that in these cases, other microorganisms were the principal pathogens or that surgical drainage was a major part of therapy.

Moxalactam-resistant anaerobic pathogens emerged in two patients treated with moxalactam and were responsible for recurrence and therapy failure. An increase in the isolation of moxalactam-resistant aerobic pathogens during therapy was observed in six patients, two of whom also acquired anaerobic resistant pathogens.

Infections in cancer patients are most often caused by aerobic gram-negative bacilli, especially when neutropenia is present (1). Systemic infection by anaerobic microorganisms is relatively infrequent under these conditions (7). No blood culture was positive in our study. These observations make doubtful whether antianaerobic antimicrobial coverage should be a part of empiric regimens to be used in cancer patients with neutropenia.

On the other hand, anaerobic infection in cancer patients represents a specific syndrome in the case of localized infections superimposed on tumor, from which both anaerobic and aerobic microorganisms can be isolated; bacteremia is infrequent under these conditions.

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