ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1982, p. 441–449
0066-4804/82/030441-09$02.00/0 Vol. 21, No. 3

Intravenous Metronidazole for Treatment of Infections Involving Anaerobic Bacteria

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Received 31 August 1981/Accepted 14 December 1981

Intravenous metronidazole was administered, either by continuous or intermittent infusion, to 20 patients with infections involving anaerobic bacteria; 14 of the 20 patients were changed to oral administration of metronidazole for completion of therapy. Six of eight patients with infections derived from oropharyngeal bacterial flora were cured; the addition of ampicillin was required in one patient, however, because of an incomplete response to metronidazole. Eight of eleven evaluable patients with infections derived from bowel flora were also cured by metronidazole or metronidazole plus an aminoglycoside. Of 93 anaerobic bacteria isolated before therapy, 89 were susceptible to 16 μg or less of metronidazole per ml. Mean plasma levels of metronidazole were 27.6 ± 11.4 μg/ml in patients receiving continuous infusions of drug and 19.9 ± 10.7 μg/ml (trough) in patients receiving intermittent infusions. Two patients developed peripheral neuropathy during therapy. Metronidazole is an effective agent for the treatment of anaerobic infections. Because metronidazole is not active against facultative and aerobic bacteria, the addition of a second antimicrobial agent may be required for the treatment of mixed anaerobic-aerobic infections.

Metronidazole, a nitroimidazole antimicrobial agent, was first used for treatment of systemic anaerobic infections by Tally et al. (19). Subsequent studies have shown metronidazole to possess excellent in vitro activity against the common anaerobic pathogens (2, 18, 22); several clinical trials with this agent have also demonstrated efficacy in treatment of anaerobic infections (6, 7, 11, 12, 15). Sanders et al. (14), however, found that metronidazole was not very effective as a single agent for treatment of pleuropulmonary infections involving anaerobes. Perlino found metronidazole less effective than clindamycin for treatment of putrid lung abscess (Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 820, 1979). Collier et al. (3), in a prospective, randomized, comparative study of clindamycin versus metronidazole (usually given with an aminoglycoside) for treatment of intraabdominal infections, found the two drugs to be equivalent in regard to efficacy and toxicity. Potential advantages of metronidazole over other agents used for treatment of anaerobic infections include consistent bactericidal activity (10, 20) and excellent penetration of drug into essentially all body tissues, fluids, and cavities (4). We have studied the efficacy of intravenous metronidazole for treatment of a variety of infections which involve anaerobic bacteria.

MATERIALS AND METHODS

Patients who had documented or suspected anaerobic infections were considered to be candidates for study. Individuals who had received prior therapy with antimicrobial agents active against anaerobes were excluded from the study unless they were clinical and bacteriological treatment failures. Informed written consent was obtained from all subjects. Collection, transport, and culture of specimens were done by previously described methods (17). Isolates were identified by standard techniques (9, 17), and the susceptibility of each anaerobe to metronidazole was determined by an agar dilution technique (17).

Metronidazole hydrochloride was administered by either continuous infusion of the drug (approximately 30 mg of drug per kg per day) in 5% dextrose in water or intermittent infusion in 250 ml of 5% dextrose in water every 6 h (30 mg of drug per kg per day). A sodium bicarbonate buffer (5 meq/500 mg of metronidazole) was added to neutralize the acidic pH of metronidazole for patients receiving intermittent therapy. Therapy was changed to oral metronidazole when improvement in clinical status permitted. Additional antimicrobial therapy (usually an aminoglycoside) was also administered whenever indicated for coverage of facultative gram-negative bacilli. Patients were seen and examined frequently by one or more of us for

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TABLE 1. Infections derived from oropharyngeal flora

Patient no.	Age (yr)	Sex	Type of infection	Antimicrobial therapy						Therapeutic response	Adverse effects
				Metronidazole			Other				
				Route[a]	Total dose (g)	Days of therapy	Agent	Total dose (g)	Days of therapy		
1	49	M	Lung abscess	i.v.* p.o.	27.5 101.3	13 45	Chloramphenicol	152	35 days before metronidazole and 43 days concurrent with metronidazole therapy	Cured; no improvement during previous 35-day course of chloramphenicol; cure effected by addition of metronidazole	Severe phlebitis, painful gynecomastia, sensory neuropathy of hands and feet (alcoholism, diabetes mellitus, and isoniazid were other possible causes of neuropathy)
3	42	M	Lung abscess	i.v.* p.o.	21.7 75.0	8 60	None			Cured	Phlebitis
10	55	M	Wound infection after resection of floor of mouth	i.v.* p.o.	4.2 51.8	3 23	Ampicillin Amikacin	52	13 days, beginning day 4 of metronidazole therapy 6 days, beginning day 11 of metronidazole therapy	Cured; ampicillin[b] added because of persistent cellulitis and persistence of streptococci in wound	None
12	60	M	Severe bilateral aspiration pneumonia, cellulitis around tracheostomy site	i.v. p.o.	42.0 29.3	17.5 13	Gentamicin	6.6	22 days, beginning with initiation of metronidazole therapy	Cured	None
16	49	M	Recurrent anaerobic pneumonia, probably due to bronchiectasis	i.v. p.o.	18.9 225	11 150	None			Failed; had excellent clinical response, but relapsed twice when metronidazole was discontinued; previously relapsed after chloramphenicol therapy[c]	None

17	45	M	Aspiration pneumonia, pulmonary tuberculosis	i.v.	28.8	12	Isoniazid Ethambutol			Cured	Increased distal latency of peroneal nerve by nerve conduction study; neuropathy not evident clinically
				p.o.	132.8	59					
23	30	M	Recurrent idiopathic oral mucosal ulcerations with severe anaerobic supra-infection	i.v.	12	6	None			Failed; complete resolution initially, but relapsed 1 week after discontinuation of metronidazole	None
				p.o.	107.3	49					
24	66	M	Empyema, pneumonia	i.v.	34.5	23	None			Cured	None
				p.o.	111	74					

[a] i.v., Intravenous; p.o., oral. Asterisk indicates that metronidazole was given by continuous infusion.
[b] All anaerobic isolates were susceptible to ampicillin.
[c] Patient refused surgery and was placed on chronic suppressive ampicillin therapy.

observation of adverse side effects and response to therapy. Peripheral leukocyte count, packed erythrocyte volume, alkaline phosphatase, bilirubin, serum glutamic oxalocetic transaminase (SGOT), and urinalysis were monitored once or twice weekly. Plasma levels of metronidazole were measured by high-pressure liquid chromatography (21) or by bioassay (Searle Pharmaceuticals Inc., Chicago, Ill.). Response to therapy was determined as follows: the patient was considered to be cured if clinical and bacteriological evidence of infection resolved; the patient was considered to be a treatment failure if either clinical or bacteriological evidence of infection failed to resolve or if relapse of infection occurred after discontinuation of therapy.

RESULTS

Twenty-five patients were entered into the study during the period from September 1977 to September 1979; five were subsequently found not to have infection involving anaerobes, and metronidazole therapy was therefore discontinued. Side effects of metronidazole were not noted in these latter five patients. The type of infection, adverse effects, and response to therapy are shown in Table 1 (8 infections derived from oropharyngeal flora) and Table 2 (12 infections derived from bowel flora). Results of culture are shown in Table 3.

An initial favorable clinical response occurred in 19 of 20 patients treated with metronidazole. One patient with a good clinical response to therapy (patient 8, Table 2) died suddenly on day 7 of therapy; autopsy was not performed, and the response to therapy, therefore, could not be evaluated. Of the 19 evaluable patients, 5 were judged to be treatment failures.

Treatment failures. Two of eight patients with infections derived from oropharyngeal flora (patients 16 and 23, Table 1) relapsed after discontinuation of metronidazole and were judged to be treatment failures. Both patients had had previous relapses after therapy with other appropriate antimicrobial agents.

Three patients with intraabdominal infections were judged to be treatment failures (patients 2, 4, and 13, Table 2). Patient 2 had antimicrobial therapy discontinued after 12 days of treatment (despite persistence of some fever) because repeat exploratory laparotomy was said not to reveal evidence of intraperitoneal infection. It could not be determined whether his subsequent intraabdominal infection was due to necrosis of the colonic mucus fistula or to purulent intraabdominal material which was overlooked during reexploration. Patient 4 had diffuse peritonitis at surgery; although he responded clinically to therapy, he was considered to be a metronidazole treatment failure because he developed a pelvic abscess which drained spontaneously through his surgical wound after discontinuation of therapy. Patient 13 was considered to be a

TABLE 2. Infections derived from bowel flora

Patient no.	Age (yr)	Sex	Type of infection	Antimicrobial therapy						Therapeutic response	Adverse effects
				Metronidazole			Other				
				Route[a]	Total dose (g)	Days of therapy	Agent	Total dose (g)	Days of therapy		
2	57	M	Peritonitis due to dehiscence of colonic anastomosis	i.v.*	34.4	12	Gentamicin	2.9	12	Failed; persistent fever during therapy. Laparotomy at end of therapy revealed necrosis of mucus fistula and omentum. Subsequently developed multiple intraabdominal and abdominal wall abscesses	None
4	27	M	Diffuse peritonitis due to cecal perforation	i.v.*	26.0	9	Gentamicin	2.2	9	Failed; signs and symptoms of infection resolved during therapy, but a large pelvic abscess drained spontaneously via the surgical incision 3 days posttherapy. Culture of the abscess contents yielded *Bacteroides distasonis* and *Bacteroides* sp; both were susceptible to metronidazole	Severe phlebitis
6	86	M	Septic arthritis of the knee	i.v.* p.o.	1.1 73.5	0.5 49	None			Cured; initial arthritis was due to *Escherichia coli, Clostridium innocuum*, and *Bacteroides thetaiotaomicron*. *E. coli* and *C. innocuum* cleared with 3 weeks of netilmicin and clindamycin therapy, but *B. thetaiota- omicron* (clindamycin minimal inhibitory concentration, ≤0.5 μg/ml) persisted	None
7	51	M	Large, infected sacral decubitus ulcer	i.v.* p.o.	5.31 51.8	2 23	Amikacin	12.0	15	Cured	Phlebitis; disseminated candidiasis documented after 7 days of therapy
8	83	M	Peritonitis due to perforation of	i.v.*	13.6	7	Gentamicin	1.6	7	Unevaluable; good clinical response, but died suddenly	None

			distal ileum							on day 7 of therapy. Autopsy not performed	
11	48	M	Large ischiorectal abscess	i.v.* p.o.	4.1 15.8	2 7	Gentamicin	2.2	9	Cured, but developed recurrence of ischiorectal abscess 2 months later	Moderately severe sensory neuropathy of feet
13	61	M	Psoas abscess and abdominal surgical wound infection	i.v.	20.7	18	Cephapirin Amikacin	162 12.2	18 18	Failed owing to presumed neurotoxicity. Good clinical response; autopsy not performed	Grand mal seizures, obtundation, hypotension, and death. Technetium brain scan and lumbar puncture did not reveal evidence of intracranial infection
14	50	M	Perirectal abscess and abdominal and colovesical fistula	i.v. p.o.	6.1 13.5	2 6	Gentamicin	2.2	7	Cured	None
15	53	M	Deep wound infection after laparotomy for appendiceal perforation	i.v. p.o.	5.2 36	2 16	None			Cured	None
18	47	M	Perirectal abscess	i.v. p.o.	4.7 3:8	2 2	Gentamicin	1.1	4	Cured	None
20	55	F	Perirectal cellulitis and abscess	i.v.	19.2	8	Amikacin Oxacillin	8.0 72.0	8 8	Cured	None
22	64	M	*F. nucleatum* bacteremia, presumably due to intraabdominal and multiple intrahepatic abscesses[b]	i.v.	20	10	None			Cured of bacteremia, but subsequently expired. Autopsy revealed endocarditis *(Staphylococcus aureus)*, gastric carcinoma, and a large, undrained, hepatic abscess	None

[a] i.v., Intravenous; p.o., oral. Asterisk indicates that metronidazole was given by continuous infusion.

[b] Pus collected from one of the hepatic abscesses during therapy was sterile, but Gram stain and gas-liquid chromatography were consistent with *Fusobacterium* species.

treatment failure because resolution of infection could not be documented.

Use of other antianaerobic agents. Three patients received agents in addition to metronidazole which possess activity against anaerobic bacteria.

Patient 1 (Table 1) had been treated for 5 weeks with chloramphenicol for an extensive right upper lobe lung abscess and pneumonia. Despite repeated therapeutic bronchoscopy to ensure good bronchopulmonary drainage, he continued to have foul-smelling, purulent sputum and intermittent fever and showed lack of improvement on serial chest roentgenograms. Soon after metronidazole therapy was added to chloramphenicol, he became afebrile; the infiltrate and cavity resolved with combined therapy.

Patient 10 (Table 1) had ampicillin added to his regimen on day 3 of therapy because of minimal improvement in a wound infection during therapy with metronidazole and amikacin and because of persistent recovery of microaerophilic streptococci from the wound. Patient 13 (Table 2) had failed to respond to therapy with cephapirin and amikacin; because of the severity of this patient's mixed infection, metronidazole was added to his regimen.

Culture and susceptibility results. A total of 121 anaerobic bacterial isolates were recovered from 19 patients in this study, including 103 that were recovered before metronidazole therapy; of the 93 pretreatment isolates which were available for susceptibility testing, 89 were susceptible to 16 μg or less of metronidazole per ml. The four resistant strains were two isolates of *Propionibacterium acnes* and one isolate each of *Eubacterium* species and an anaerobic gram-positive coccus. In addition, a resistant *Lactobacillus* sp. was recovered from patient 10 on day 2 of therapy. Cultures were not performed on patient 23 because of inability to avoid contamination of the specimen by normal flora of the oral cavity.

Metronidazole serum levels. The mean plasma level of metronidazole ± standard deviation for patients receiving continuous infusions of drug was 27.6 ± 11.4 μg/ml (19 determinations for eight patients); the range of values was 6.1 to 50.5 μg of drug per ml. Plasma levels of metronidazole were in excess of 16 μg/ml in all patients who received continuous infusion of drug, except for a value of 14.7 μg/ml on day 1 of therapy in patient 4 and a value of 6.1 μg/ml in patient 3. The latter patient was also receiving Dilantin (diphenylhydantoin sodium), which may have induced an increased rate of hepatic metabolism of metronidazole (21). His peak serum level 6 days after being changed to oral therapy was only 5.5 μg of metronidazole per ml.

TABLE 3. Bacteria recovered from infection before metronidazole therapy

Bacterium	No. recovered
Anaerobes	
Bacteroides fragilis	5
B. thetaiotaomicron	6
B. vulgatus	1
B. melaninogenicus subsp. *intermedius*	6
B. melaninogenicus subsp. *melaninogenicus*	3
B. melaninogenicus (not identified to subspecies level)	1
B. asaccharolyticus	3
B. bivius	1
B. oralis	9
B. ruminicola subsp. *brevis*	9
Bacteroides sp.	4
Fusobacterium naviforme	1
F. nucleatum	6
Veillonella parvula	1
Peptococcus asaccharolyticus	1
P. magnus	1
P. prevotii	4
Peptostreptococcus anaerobius	2
P. micros	4
Anaerobic gram-positive coccus	1
Anaerobic *Streptococcus*	2
Clostridium difficile	1
C. malenominatum	1
C. paraperfringens	1
C. perfringens	2
C. ramosum	4
Clostridium sp.	2
Bifidobacterium adolescentis	1
Bifidobacterium sp.	1
Lactobacillus catenaforme	2
Lactobacillus sp.	2
Eubacterium contortum	1
Eubacterium sp.	11
Propionibacterium acnes	2
Anaerobic gram-positive bacillus	2
Facultatives-Aerobes	
Staphylococcus, coagulase negative	1
α-Hemolytic *Streptococcus*	11
β-Hemolytic *Streptococcus*	3
Group D *Streptococcus*	5
Streptococcus sp.	2
Neisseria lactamica	1
Corynebacterium sp.	1
Diphtheroids	2
Haemophilus influenzae	1
Escherichia coli	9
Enterobacter cloacae	2
Klebsiella pneumoniae	2
Morganella morganii	1
Proteus mirabilis	3
Pseudomonas aeruginosa	1
P. maltophilia	2

Trough plasma levels (but not peak levels) were obtained routinely in patients receiving intermittent infusions of metronidazole. Mean trough level ± standard deviation was 19.9 ±

10.7 μg of drug per ml (13 determinations for nine patients); the range of values was 4.8 to 40.1 μg of drug per ml. All trough levels, except for that in patient 14, were greater than 10 μg/ml. Patient 1 had a serum trough level of 22.4 μg/ml and a peak level of 55.3 μg/ml at 15 and 17 days, respectively, after being changed to oral metronidazole therapy.

Metronidazole toxicity. Phlebitis developed in four of the nine patients receiving continuous infusion of metronidazole and was severe in two patients. Both had received a continuous infusion of unbuffered metronidazole. Phlebitis was not seen after the protocol was changed to intermittent infusion of metronidazole buffered with sodium bicarbonate. Peripheral sensory neuropathy developed in patients 1 and 11 during therapy and was confirmed by nerve conduction studies; both patients had received continuous infusions of the drug. Possible contributing factors in patient 1 were diabetes mellitus, a history of ethanol abuse, and concomitant administration of isoniazid. Patient 13 (Table 2) developed obtundation and seizures during metronidazole therapy. At the time of onset of neurological symptoms, pertinent laboratory values were bilirubin, 13.5 mg/dl; alkaline phosphatase, 342 IU/dl (normal, ≤115 IU/dl); SGOT, 82 IU/dl (normal, ≤36 IU/dl); glutamic pyruvate transaminase, 187 IU/dl (normal, ≤32 IU/dl); lactic dehydrogenase, 467 IU/dl (normal, ≤225 IU/dl) and creatinine, 4.3 mg/dl. Because of the interference of metronidazole with the colorimetric test for SGOT, the value of 82 IU/dl was thought to be spuriously low; the SGOT level 1 week before the onset of neurological deterioration was 21 IU/dl.

The only laboratory abnormality attributable to metronidazole therapy was a consistent perturbation of SGOT; this test was done by an automated system (SMA 12/60; Technicon Corp., Inc., Tarrytown, N.Y.). Of the 20 patients, 8 had SGOT levels reported to be zero during therapy. In six others, the SGOT levels decreased to from 7 to 41% of baseline values; this decline could not be attributed to a change in clinical status. Serial SGOT determinations were unaffected in three patients, and serial values were unavailable in three others.

DISCUSSION

We and others (6, 7, 11, 12, 15) have found metronidazole to be an effective agent for treatment of infections involving anaerobic bacteria. The lack of activity of metronidazole against facultative bacteria, however, is an indication for appropriate additional agents for mixed anaerobic-aerobic infections. The response of infection derived from the oropharyngeal flora was favorable in all eight patients in our study. The two patients (16 and 23, Table 1) in this group who relapsed after discontinuation of metronidazole had had prior relapses after other antimicrobial therapy; these relapses after metronidazole treatment in all likelihood reflect the nature of the underlying disease rather than the ineffectiveness of metronidazole. An important limitation of metronidazole, however, is its poor activity against microaerophilic streptococci. The slow response of patient 10 to therapy was thought to reflect this; his infection responded significantly when ampicillin was added to the regimen.

The response of patients with intraabdominal infections (Table 2) was relatively poor when compared with all other types of infection. Because intraabdominal infection was generally the most severe of all types studied, we believe that randomized comparative studies of metronidazole with agents such as clindamycin and chloramphenicol are needed in order to assess the potential role of metronidazole for treatment of serious anaerobic infections derived from bowel flora. Smith et al. (16) have performed a prospective, randomized, double-blind comparison of metronidazole and clindamycin (both were given in conjunction with tobramycin) for treatment of intraabdominal infections. Although these authors concluded that response to therapy in both groups was not statistically different, both the metronidazole and clindamycin groups included patients from whom anaerobes were not recovered. Of patients from whom anaerobes were recovered, a good or fair response occurred in 79% of those treated with metronidazole and in 85% treated with clindamycin. The data from Collier et al. (3) indicate that metronidazole is as effective as clindamycin for the treatment of intraabdominal infections involving anaerobes.

The response of patient 6 to metronidazole merits mention. Although this patient was not cured of infection with 3 weeks of clindamycin therapy, both a prompt bacteriological and clinical response were effected by metronidazole. It is possible that the bactericidal activity of metronidazole was important in this regard.

Peripheral neuropathy, an adverse effect of metronidazole which has been reported previously (4), occurred in two of our patients. One of these patients had several possible predisposing causes, as noted above. In addition, patient 13 (Table 2) developed obtundation and seizures which could not be attributed to a metabolic disturbance or to central nervous system infection. Although seizures and obtundation have been reported only in patients receiving extremely large (radiosensitizing) doses of metronidazole (5, 8), the high plasma trough levels of metronidazole (40.1 and 38.9 μg of drug per ml),

despite reduction in drug dosage, suggest that neurotoxicity might have occurred; these high trough levels of drug were thought to be a consequence of combined renal and hepatic dysfunction. It is not known whether metronidazole or metronidazole metabolites are responsible for producing peripheral neuropathy and central nervous system toxicity. Because the drug appears to be largely metabolized by the liver, it would seem prudent to avoid the use of metronidazole in patients with severe hepatic dysfunction. Although the drug and its metabolites are excreted primarily by the kidneys, the risk of toxicity associated with renal dysfunction is not known (1).

Phlebitis was a serious problem during the early phase of the study, when unbuffered metronidazole was given by continuous infusion. Phlebitis was not noted subsequent to the addition of a buffering solution and the institution of intermittent infusion of metronidazole. The spuriously low SGOT levels that may occur during therapy with metronidazole are troublesome; Rissing et al. (13) reported that this problem may be avoided by use of the Technicon SMAC system for SGOT determination.

Of the antimicrobial agents which are available for treatment of anaerobic infections, only metronidazole, chloramphenicol, and clindamycin are active against virtually all isolates of the *Bacteroides fragilis* group. Certain other agents, including cefoxitin, carbenicillin, and ticarcillin, possess good activity against many anaerobes, although 5 to 10% of *B. fragilis* isolates may be resistant. Metronidazole and chloramphenicol are also essentially always active versus other gram-negative anaerobic rods and clostridia, some of which may be resistant to clindamycin. The consistent bactericidal activity of metronidazole suggests the potential superiority of this agent for the treatment of certain types of infection, such as anaerobic meningitis, brain abscess, and endocarditis, and perhaps infections in immunosuppressed hosts. Metronidazole is not active in vitro against facultative bacteria; therefore, treatment of mixed anaerobic facultative infections with metronidazole would usually necessitate the addition of a second antimicrobial agent.

Selection of an agent for other types of anaerobic infections requires a knowledge of the comparative efficacies and toxicities of potentially useful agents. We believe that such information can be gained only by prospective, randomized, comparative studies of metronidazole with other agents for the treatment of serious anaerobic infections.

ACKNOWLEDGMENTS

We thank P. Wideman, R. Kwok, W. Carter, and R. Rolfe for their technical assistance, M. Ma for helping to coordinate administration of metronidazole, and K. Ishii for typing the manuscript.

This study was supported by a grant from G. D. Searle & Co. and by Veterans Administration Medical Research funds.

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