Treatment of Anaerobic Bacterial Infections with Clindamycin-2-Phosphate

MATTHEW E. LEVISON, JOSE L. BRAN, AND KRISTEN RIES

Division of Infectious Diseases, The Medical College of Pennsylvania and the Veterans Administration Hospital, Philadelphia, Pennsylvania 19129

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Thirty-five patients with a variety of serious infections caused by anaerobic bacteria responded to clindamycin. Cure was achieved in 27 of the 32 patients with pleuropulmonary and intra-abdominal infections. Mean serum concentrations of clindamycin for the 8 h after intramuscular administration of clindamycin in these patients were at least 2.5 times the minimal inhibitory concentration of clindamycin for more than 90% of anaerobes. This experience suggests that clindamycin is an excellent and relatively safe antibiotic for treatment of infection caused by anaerobes when combined with surgery (when indicated) or other antibiotics active against aerobic gram-negative bacilli, if present.

Clindamycin and chloramphenicol (1, 3, 13, 14, 17) have excellent in vitro antibacterial activity against most strains of anaerobes, including Bacteroides fragilis. However, chloramphenicol is toxic for the hematopoietic tissues, especially with the doses and duration of therapy required for severe anaerobic bacterial infection. Recent clinical studies have reported favorable results from clindamycin therapy in the treatment of a variety of anaerobic bacterial infections (1, 8, 12).

The present study was undertaken to determine the efficacy of clindamycin-2-phosphate in the treatment of anaerobic bacterial infection.

MATERIALS AND METHODS

Laboratory studies. Specimens were obtained in syringes from which the air was expelled and were processed within 20 min. Each specimen was Gram stained and plated by using a semiquantitative technique with which bacterial growth can be classified as <10³/ml or ≥10³/ml (19). The plates were incubated aerobically, microaerophilically in a candle jar and anaerobically in the GasPak system (BBL) by techniques previously described (19).

Susceptibility to clindamycin and other antibiotics was determined by a disk-agar diffusion method (20) with the GasPak system. The concentration of clindamycin bioactivity in serum was determined by an agar diffusion method using paper disks (18).

Clinical studies. Thirty-five patients were treated with clindamycin-2-phosphate (300 to 600 mg) every 8 h intramuscularly (i.m.) (in 25 patients), intravenously (i.v.) (in 4 patients) or both i.v. and i.m. (in 6 patients). Surgery and other supportive measures were performed as indicated. All patients had infections caused by obligate anaerobic bacteria with or without aerobic bacteria present. Patients who had received previous antibiotic therapy were accepted for the study only if there had been neither clinical nor bacteriological response. In patients with aerobic gram-negative bacilli also present, another antibiotic (usually gentamicin) was given with clindamycin, but in each case the predominant anaerobic organisms were resistant in vitro to the other antibiotic. Specimens for bacterial cultures were obtained before therapy was started and at appropriate intervals to evaluate bacteriological response. Care was taken in the collection of specimens to avoid contamination by normal flora. Specimens were obtained by percutaneous transtracheal aspiration in patients with pulmonary infection and by deep needle aspiration from abscesses or cellulitis.

Serial determinations of hemoglobin, hematocrit, white blood cell count and differential, urinalysis, blood urea nitrogen and serum creatinine, alkaline phosphatase, bilirubin, glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), and creatinine phosphokinase (CPK) were obtained. Informed consent was obtained from all patients.

RESULTS

Bacteriology. In each of the 35 patients, one to five anaerobic microorganisms were isolated in concentrations of 10³/ml or more. Anaerobic gram-negative bacilli were most often isolated (51% of anaerobic isolates and 42% of all isolates). In 7 of 16 patients with pleuropulmonary and 11 of 16 patients with intra-abdominal
infections, aerobes also were isolated in concentrations of \(10^7/\text{ml}\) or more. In mixed cultures, anaerobes predominated. In most of the patients with mixed pulmonary infections, oropharyngeal flora (such as Neisseria sp., Streptococcus viridans, and diphtheroids) were isolated. Enterobacteriaceae were isolated in one patient with pleuropulmonary and in eight with intra-abdominal infections. Three patients had, in addition, anaerobic bacteremia: two with B. fragilis, and one with B. fragilis and anaerobic gram-positive cocci. With a 2-\(\mu\)g clindamycin disk, zones of inhibition were 17 mm or greater for all of the anaerobic bacteria which were isolated in concentrations of \(\geq 10^9/\text{ml}\) before clindamycin therapy. No zone of inhibition occurred with an anaerobic gram-negative bacillus isolated from a repeat transtracheal aspirate in a patient who only partially responded to clindamycin.

**Serum clindamycin concentrations.** Mean serum concentrations of clindamycin (23 determinations in 5 patients) on the 6th to the 16th day of clindamycin therapy i.m. in doses of 12 to 42.9 mg per kg per day were 5.5 \(\mu\)g/ml (range, 4.2 to 7.0) at 1 h, 7.4 \(\mu\)g/ml (range, 4.2 to 12.2) at 2 h, 4.9 \(\mu\)g/ml (range, 3.4 to 6.8) at 4 h, 4.0 \(\mu\)g/ml (range, 3.4 to 5.2) at 6 h, and 4.1 \(\mu\)g/ml (range, 1.9 to 8.0) at 8 h after administration.

**Clinical studies: pulmonary infections.** Sixteen patients had pleuropulmonary infections, four had infiltrative pneumonia, three had necrotizing pneumonia (infiltrative pneumonia with multiple areas of excavation), five had pulmonary abscess, and one had infected cystic bronchiectasis. Three patients had empyema, two with pulmonary abscesses and one with a parenchymal infiltrate.

The average age of these 16 patients was 46 years (range, 16 to 66). All had predisposing illnesses which favored aspiration. In addition, one patient with empyema had a penetrating wound of the chest. Clindamycin was administered in an average dose of 15.8 mg per kg per day (range, 13.9 to 18.7) for 11.3 days (range, 9 to 15) for infiltrative pneumonia, and 23 mg per kg per day (range, 11 to 42.9) for 23.3 days (range, 15 to 29) for other pleuropulmonary infections. Emphyema was also treated with thoracentesis in one patient and thoracotomy tube drainage in two patients. Gentamicin initially was administered concurrently with clindamycin to four patients for 3 days to 2 weeks. The predominant anaerobes in each of the latter patients were resistant in vitro to gentamicin.

Of the 14 initially febrile patients, the mean duration of fever after initiation of clindamycin was 3.5 days in infiltrative pneumonitis and 6.5 days in other pleuropulmonary infections. Foul-smelling sputum production rapidly abated in those with lung abscess. In 7 of 11 patients with pulmonary infection, a culture of a repeat transtracheal aspirate revealed elimination of the predominant anaerobic pathogens 4 days to 3 weeks after initiation of clindamycin therapy. Persistence or ingrowth of microorganisms in transtracheal aspirates occurred in four patients, three of whom had tracheostomies, but was clinically significant in only two. In one of these, Pseudomonas aeruginosa necrotizing pneumonia occurred after a satisfactory clinical, bacteriological, and radiographic response of an infiltrative pneumonitis in one patient with a tracheostomy on mechanically assisted ventilation. In the other, a lung abscess resolved only partially during 3 weeks of clindamycin therapy, and ingrowth of an anaerobic gram-negative bacillus resistant to clindamycin was discovered; the abscess cleared completely after 1 week of ampicillin.

The infecting microorganisms were eliminated in the three patients with empyema, one of whom had bacteremia due to B. fragilis and anaerobic gram-positive cocci. One patient with anaerobic empyema treated by thoracotomy tube drainage after initial satisfactory response developed secondary Klebsiella pneumoniae empyema which responded to surgical drainage. Complete radiographic resolution or minimal residual lesions were noted during clindamycin therapy in 11 of the 16 patients. Three patients had less impressive radiographic responses but showed marked resolution 2 months to 2 years after discontinuation of clindamycin without additional therapy. Two additional patients with lung abscess had only partial resolution when the course of clindamycin therapy was interrupted. One of the two patients who had partial resolution of a lung abscess after 3 weeks of clindamycin cleared completely after 1 week of ampicillin therapy. One patient with partial resolution of a lung abscess after 2 weeks of clindamycin therapy had a fatal massive hemoptysis secondary to bronchogenic carcinoma; no pus was present in the cavity at autopsy.

**Intra-abdominal infections.** Of the 16 anaerobic intra-abdominal infections, six followed hysterectomies (five of which were accompanied by abdominal wound infections), one was an infected dermoid cyst of the ovary, one was probably secondary to an intrauterine device for contraception, three followed appendectomy, three followed ileocolostomy, one followed traumatic rupture of the duodenum, and one occurred during 5-fluorouracil treatment of an adenocarcinoma of the sigmoid colon.
The average age was 46 years (range, 11 to 73). The average dose of clindamycin was 21.9 mg per kg per day (range, 8.7 to 35.7) for an average of 14.9 days (range, 6 to 40). Eight patients in whom anaerobic organisms were mixed with aerobic gram-negative bacilli were treated with gentamicin (six patients) or gentamicin and ampicillin (two patients) to which the predominant anaerobes were resistant.

All patients were severely ill despite prior therapy to seven patients with parenteral antibiotics other than clindamycin. Two patients had _B. fragilis_ bacteremia. All drained spontaneously or required surgical incision and drainage.

Six patients became afebrile coincident with drainage of intra-abdominal abscesses which was performed after or shortly before initiation of clindamycin therapy. Two patients remained febrile during therapy and became afebrile within 48 h after clindamycin was discontinued; the fever was attributed to clindamycin in one patient and either clindamycin, ampicillin, or gentamicin in the other. In the remaining eight patients, the mean duration of fever after initiation of clindamycin was 9.6 days (range, 6 to 20).

Thirteen of the 16 patients responded favorably with closure of wounds, although an enterocutaneous fistula persisted in two patients with colon carcinoma. Upon clindamycin therapy, three patients formed new abscesses after initial improvement from which a mixed flora was isolated, including clindamycin-sensitive anaerobes. All three patients responded favorably, one patient to surgical drainage alone, another patient to surgical drainage and ampicillin therapy, and the third patient to surgical drainage and continued clindamycin therapy.

One patient developed an episode of _K. pneumoniae_ bacteremia while receiving clindamycin and gentamicin.

Soft tissue and bone infections. Three patients had soft tissue or bone infection. One patient with a mixed anaerobic-aerobic necrotizing cellulitis responded favorably to surgery and clindamycin, but died of cardiac arrest on the 16th day of therapy.

A diabetic patient who had _B. fragilis_ osteomyelitis of the fourth and fifth right metatarsal bones and a neurotropic ulcer was treated with clindamycin, given 500 mg i.m. three times daily for 2 weeks and 450 mg orally three times daily for 6 weeks. Soft tissue involvement improved and periosteal elevation decreased although osteolytic changes on radiography were only minimally improved 4 months and 1 year later. Another patient with squamous cell carcinoma of the pharynx who had been treated with a radical neck dissection and radiation 2 years previously had osteomyelitis of the temporal bone due to a mixture of anaerobes, _Enterobacteriaceae_, and _P. aeruginosa_. He was treated with clindamycin, given 300 mg three times daily intramuscularly for 5 weeks with defervesence within 1 week, marked decrease in purulent drainage from the external auditory canal and a pharyngocutaneous fistula, and improvement of soft tissue involvement. However, the destructive bone lesion failed to improve at the end of therapy. Foul-smelling drainage in the area returned 3 months after discontinuation of clindamycin, but further antibiotic therapy was refused. He died 2 months later of noninfectious complications. Neither patient had sequestra demonstrated radiographically.

Adverse reactions. Mild elevations in SGOT values which either were normal or mildly elevated on initiation of clindamycin occurred in 13 patients, 8 of whom had elevation of other liver function tests before clindamycin therapy. Mild elevation in SGPT, associated with prior elevation of other liver function tests, occurred in five patients. Elevations of alkaline phosphatase occurred in 10 patients, 4 of whom had prior elevations of other liver function tests. Transient serum creatinine elevation occurred in 6 of 13 patients who concomitantly received gentamicin. Mild CPK elevations occurred in 10 of 31 patients who received intramuscular clindamycin. Two patients complained of pain at the site of i.m. administration, but only one had to be changed to i.v. administration. Presumed drug fever was seen in two patients.

Only one patient had a severe, possibly drug-related, reaction. One day after stopping a 12-day course of therapy with clindamycin (25.5 mg per kg per day i.v.) and gentamicin (80 mg i.m. every 8 h), she developed a transient generalized maculopapular erythematous rash, at which time a mild elevation of SGOT was noted. Liver function tests became progressively more abnormal. Peak values were: 1,320 U/liter of SGOT (normal, 7 to 40) on the 10th day post-treatment; 680 U/liter of SGPT (normal, 1 to 28) on the 26th day post-treatment; 5.6 mg% of total bilirubin (2.1 mg% direct and 3.5 mg% indirect); and 460 U/liter of alkaline phosphatase (normal, 30 to 85) on the 33rd day post-treatment. Bilirubin returned to normal after 2.5 months and alkaline phosphatase returned to normal after 3.5 months, but SGOT and SGPT remained elevated at 61 and 47 U/liter, respectively, after 5 months. This patient was transfused 3 weeks and 1 week before
onset of hepatitis, but serum hepatitis-associated antigen determination was negative during the illness. Liver biopsy was not performed.

**DISCUSSION**

In three previously published reports evaluating clindamycin in the treatment of anaerobic bacterial infections, the anaerobic isolates included a variety of bacteria; about 50% of specimens grew a mixture of anaerobes, and 50% grew a mixture of anaerobes and aerobes, usually *Enterobacteriaceae* (1, 8, 12). These results were similar to that of this study.

Clindamycin, when administered parenterally as the phosphate ester, is rapidly hydrolyzed to microbiologically active free clindamycin (W. Morozowich, D. J. Lamb, R. M. De Haan, and J. E. Gray, Abstr. Annu. Meet. Acad. Pharmacut. Sci., p. 63, 1970). In this study, mean serum levels during the 8 h after i.m. administration of clindamycin were greater than 4.0 µg/ml, and the mean peak serum level was 7.4 µg/ml. The lowest concentration in any patient was 1.9 µg/ml. These serum concentrations are similar to those previously reported (7) and are in excess of the minimal inhibitory concentration (1.6 µg/ml) for 90 to 100% of most pathogenic anaerobes, including *B. fragilis* (1, 3, 13, 14, 17).

Forty-nine of 51 previously reported patients with a variety of anaerobic bacterial infections responded favorably to clindamycin (1, 8, 12). In our series, all infections responded, and cure of the infection caused by anaerobes was achieved in 14 of 16 pleuropulmonary and 13 of 16 intra-abdominal infections.

Three intra-abdominal infections relapsed with abscesses due to multiple organisms including clindamycin-sensitive anaerobes. Lack of clinical response of intra-abdominal infections associated with persistence of anaerobes sensitive in vitro to the antibiotics being used has been noted with tetracycline (12), penicillin (2, 4), and chloramphenicol (12, 13; H. Thadepalli, S. Gorbach, and J. Bartlett, Abstr. Intersc. Conf. Antimicrob. Ag. Chemother., 13th, Washington, D.C., abstr. no. 117, 1973). Bacterial persistence can be due to enormous numbers of slowly growing bacteria, supplicative thrombophlebitis, or the presence of necrotic material which could lessen the effect of an antibiotic. Such situations probably require surgical intervention. In fact, six patients in the present series became afebrile within 24 h after drainage was performed after or shortly before initiation of clindamycin treatment. Although surgical debridement of necrotic tissue and drainage of closed-space anaerobic infections is fundamental and occasionally has been sufficient to effect a cure (16), antibiotics usually are required in the treatment of anaerobic infections, especially when bacteremia is present. For example, the mortality rate in bacteroides sepsis has declined from 83% (11) in the pre-antibiotic era to 20 to 40% (10, 11, 15, 21) at this time.

The duration of clindamycin therapy was prolonged in some patients in the present and previous series (1, 8, 12) because of the tendency of these infections to relapse and to be associated with extensive tissue necrosis, not all of which is accessible to surgical drainage. However, in some patients with pleuropulmonary infection, clindamycin therapy need not be continued until resolution of the roentgenologic abnormalities. For example, in this study, resolution was found to continue despite discontinuation of clindamycin. Although clindamycin alone has been reported to be sufficient to treat some patients with infections due to a mixture of *Enterobacteriaceae* and anaerobes (12; H. Thadepalli and S. Gorbach, Abstr. Intersc. Conf. Antimicrob. Ag. Chemother., Atlantic City, abstr. no. 135, 1972), in the present and previous series (1, 8, 12) these patients were treated with gentamicin in addition to clindamycin because the aerobes were thought to be significant pathogens. For example, one patient with an intra-abdominal abscess in which *K. pneumoniae* was present in mixed culture with anaerobes developed *K. pneumoniae* bacteremia. In addition, gentamicin has in vitro antibacterial activity against some anaerobes, such as *B. melaninogenicus*, and anaerobic gram-positive cocci and sporeless rods, although most anaerobes are resistant (17).

Adverse reactions to clindamycin have not been major problems. Occasional pain at the site of i.m. administration, transient mild elevation of SGOT, SGPT, alkaline phosphatase, and CPK, skin rashes, and drug fever occurred in the present and previous reports (1, 7, 8, 12). Many of the patients in the present report with abnormal SGOT, SGPT, and alkaline phosphatase determinations had either chronic alcoholism or intra-abdominal abscesses with possible metastatic liver infection. Mild diarrhea (1, 7), eosinophilia (8), and phlebitis on i.v. administration (8) also have been reported. Colitis (5) and the Stevens-Johnson syndrome (9) have rarely been associated with oral clindamycin administration. Icteric hepatitis possibly associated with clindamycin administration occurred in one patient in this study and has been
reported previously in one other patient (6).

Although controlled prospective studies are not available, the present experience suggests that clindamycin is at least comparable to penicillin, tetracycline, or chloramphenicol, which are well established as effective therapy for anaerobic infections (excluding central nervous system infections where penetration of clindamycin is poor). In addition, clindamycin has the advantage of a wider spectrum of antibacterial activity against anaerobes than does penicillin or tetracycline. This is essential when treating infections from which all of the significant pathogens may not be cultured because of initially inaccessible lesions or inadequate anaerobic cultivation. Clindamycin also has relatively little toxicity or side effects and has an effective oral as well as parenteral preparation.

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LITERATURE CITED