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Parenteral Clindamycin Phosphate: Pharmacology with Normal and Abnormal Liver Function and Effect on Nasal Staphylococci

D. N. WILLIAMS,[1]* KENT CROSSLEY,[2] CAROL HOFFMAN, AND L. D. SABATH[1]

Channing Laboratory, Thorndike Memorial Laboratory, Harvard Medical Unit, and Department of Medical Microbiology, Boston City Hospital, Boston, Massachusetts 02118, and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02118

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Parenteral clindamycin was evaluated in 41 patients with a variety of infections. The four major findings were as follows. (i) Five hours after the intravenous administration of 600 mg of clindamycin, the mean serum concentration in patients with "moderate to severe" hepatic dysfunction was 24.3 μg/ml, and in those with normal liver function it was 8.3 μg/ml ($P < 0.02$). This suggests that the dose of clindamycin might be modified in patients with liver disease. (ii) There was a positive association between the 5-h serum clindamycin level and the degree of elevation of the serum glutamic oxaloacetic transaminase. (iii) No significant side effects were observed. Of 24 patients with preexisting hepatic dysfunction, 5 showed deterioration and 5 showed improvement of liver function during therapy. (iv) Whereas all pre-treatment isolates of *Staphylococcus epidermidis* from the anterior nares were susceptible to clindamycin, 6 of 9 post-treatment isolates were resistant, most probably due to selection of resistant organisms.

Clindamycin (7-chloro-7-deoxylincomycin) is a derivative of lincomycin and is 4 to 16 times as active as the parent compound (9). It has been used successfully in the treatment of gram-positive coccal infections and in the treatment of disease caused by anaerobic organisms for which many consider it the preferred drug (2, 5).

Clindamycin-2-phosphate, which is rapidly hydrolyzed in the body to clindamycin, was administered parenterally to 41 patients with a variety of infections. This report compares the concentrations of clindamycin obtained in various body fluids in patients with and without hepatic dysfunction, documents changes in liver function occurring during the course of treatment, and records changes in the antibiotic susceptibility of nasal staphylococci before and after therapy.

MATERIALS AND METHODS

The 41 in-patients were 17 to 90 years old. Clindamycin phosphate was selected for therapy because of previous penicillin allergy or when anaerobic infections were suspected. Thirty-five patients (85%) were treated intravenously and 6 (15%) were treated intramuscularly with clindamycin phosphate. The individual daily dosage ranged from 600 to 4,800 mg (5.1 to 52.8 mg/kg per day), one-fourth that amount usually being given every 6 h. Twenty-five patients were treated with either 300 or 600 mg every 6 h. There was no significant difference in the dose of clindamycin between those with and without hepatic dysfunction. The duration of parenteral therapy was from 2 to 15 days (mean, 6 days). For intravenous administration, the drug was diluted in 150 ml of 5% dextrose and infused over a 30-min period.

Patients were observed for adverse effects clinically and by serial determination of hematocrit, leucocyte count and differential, blood urea nitrogen, urinalysis, serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase, alkaline phosphatase, total bilirubin, protein, albumin, and prothrombin time. In five patients, direct and indirect serum bilirubin and haptoglobin determinations were made.

Prior to therapy, appropriate bacteriological specimens were taken for culture and, whenever possible, serum levels of clindamycin were obtained one and 5 h after drug administration. In 15 patients urine samples were obtained, and in 2 patients bile samples were obtained; these specimens were diluted with phosphate buffer at pH 6.0 before assay. In one patient, maxillary bone was obtained during an operation, the bone fragment was ground, and the drug was extracted in phosphate buffer at pH 8.0 before assay.

[1] Present address: Department of Medicine, University of Minnesota, Minneapolis, Minn. 55455.

[2] Present address: Fitzsimons Army Medical Center, Denver, Colo. 80240.

Classification of liver disease. Twenty-four patients had deranged liver function tests (LFTs) prior to therapy, whereas the remaining 17 had normal pre-treatment LFTs. For the purpose of this study, patients were divided into those with "mild" and "moderate to severe" degrees of hepatic dysfunction as follows. Mild hepatic dysfunction was defined as either a total serum bilirubin level of between 1.3 and 3.0 mg/100 ml or an elevated SGOT level of between 50 and 100 mIU/ml (upper limit of normal for total serum bilirubin was 1.2 mg/100 ml and for SGOT 40 mIU/ml). Of the 13 patients so classified, 6 satisfied the criterion for bilirubin elevation, 10 satisfied it for SGOT elevation, and 3 satisfied both criteria. Moderate to severe hepatic dysfunction was defined as either a total serum bilirubin level of greater than 3.0 mg/100 ml or an elevated SGOT level of greater than 100 mIU/ml. Eleven patients were thus classified, 7 of whom satisfied the criterion for bilirubin elevation, 7 satisfied it for SGOT elevation, and 3 satisfied both criteria.

Nasal staphylococcal isolates. Seven patients had swabs taken of the anterior nares both before and 5 days after the commencement of clindamycin therapy. An additional 5 patients had a single swab taken either before or after antibiotic therapy. The nasal staphylococcal isolates were speciated by morphology and their ability to ferment mannitol and produce coagulase. Differentiation of isolates of *Staphylococcus epidermidis* was made by colonial morphology, antibiotic susceptibility, and pattern of synergistic haemolysis with β-toxin-producing *S. aureus* on 2% sheep blood agar (L. D. Sabath, S. J. Wallace, and A. Kane, personal communication). Phage typing and biotyping of these isolates were carried out by C.P.A. van Boven of Rotterdam, Netherlands.

Evidence of a clindamycin-destroying enzyme in resistant organisms was sought by the Haight-Finland modification (6, 7) of the Gots test, substituting clindamycin in the agar for penicillin.

Antibiotic susceptibility testing: antibiotic assay. The clindamycin susceptibility of 13 clinical isolates of *S. aureus* and 19 staphylococcal isolates from the anterior nares was determined on Mueller-Hinton agar in vitro by a twofold agar dilution technique using a Steers inocula replicator (4). Overnight (18-h) cultures in Mueller-Hinton broth diluted 10^{-3} were used as inocula.

Antibiotic concentrations were determined by an agar diffusion method with *Sarcina lutea* SKF 1360 as assay organism. Clindamycin activity in the presence of gentamicin or kanamycin was measured by the agar diffusion method with *Clostridium perfringens* as test organism (10). When a penicillin or cephalosporin was used concurrently or in the week preceding clindamycin therapy, the patient's serum was incubated with β-lactamase II prior to assay. The standard powder (clindamycin hydrochloride) for susceptibility testing and sterile material for parenteral injection were supplied by the Upjohn Company, Kalamazoo, Mich.

Statistical methods. The mean concentrations of clindamycin levels in various situations were compared by Student's *t* test. The association between the serum clindamycin and the corresponding SGOT levels was determined by computer analysis of the goodness of fit.

RESULTS

Concentration of clindamycin in serum. The concentration of clindamycin in serum 1 to 2 h after intravenous administration of 600 or 300 mg was not statistically different in patients with and without hepatic dysfunction ($P = 0.2$ and 0.5, respectively). The mean value after administration of 600 mg was 20.9 μg/ml (seven determinations with a range of 8.4 to 43.5 μg/ml) in patients with hepatic dysfunction and 16.2 μg/ml (six determinations, range 6.2 to 25.6 μg/ml) in those with normal liver function. Similarly, after a 300-mg dose the mean value was 19.5 μg/ml (eight determinations, range 11.5 to 33.7 μg/ml) in those with hepatic dysfunction and 15.0 μg/ml (four determinations, range 11.5 to 15.7 μg/ml) in those with normal liver function. However, 5 h after the intravenous administration of 600 mg of clindamycin, the mean serum concentration in patients with moderate to severe hepatic dysfunction was 24.3 μg/ml (seven determinations, range 8.0 to 40.8 μg/ml) and 8.3 μg/ml (six determinations, range 1.2 to 19.5 μg/ml) in those with normal liver function ($P < 0.02$). A similar trend was noted 5 h after the administration of 300 mg of clindamycin, the mean value of patients with hepatic dysfunction being 13.3 μg/ml (four determinations, range 3.0 to 18.8 μg/ml) and 5.4 μg/ml (three determinations, range 1.1 to 9.8 μg/ml) in those with normal liver function, but these results were not significantly different ($P = 0.2$). Eighty percent of sera for clindamycin assay were obtained during the first 4 days of therapy. No difference in the duration of clindamycin therapy prior to serum antibiotic assays was found between those with and without hepatic dysfunction.

The concentration of clindamycin in serum 5 h after intravenous administration was measured in 14 patients, in one of whom three determinations were made. Seven of these patients had some degree of hepatic dysfunction. Analysis revealed a positive association between the serum clindamycin level 5 h after intravenous administration and the degree of elevation of the SGOT level (regression coefficient, 0.72; $P < 0.0005$) (Fig. 1). No positive association between serum clindamycin level and other parameters of liver function (total bilirubin, lactic acid dehydrogenase, and alkaline phosphate) was found.

Concentration of clindamycin in urine. Concentration of clindamycin in urine collected

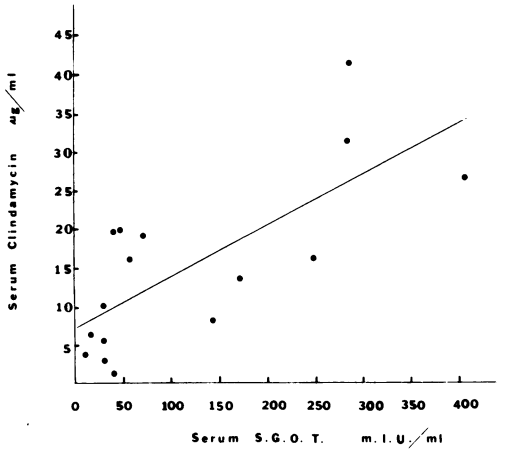

FIG. 1. *Correlation between SGOT levels and concentration of clindamycin in serum 5 h after intravenous dose. Regression coefficient, 0.72 ($P < 0.005$).*

over 4- or 6-h periods ranged from 66 to 400 µg/ml (mean, 207 µg/ml) (Fig. 2). There was no significant difference in the amount of drug recovered in the urine among the eight patients with and the seven patients without hepatic dysfunction (respective mean values of 26.5% recovery of the dose compared with 15.5%). Further analysis revealed that those with moderate to severe and mild hepatic dysfunction had 33 and 19.8% recovery in the urine, respectively.

Concentration of clindamycin in other body fluids and tissue. Concentration of clindamycin in bile collected over a 24-h period via a T-tube in the common bile duct was 48 and 55 µg/ml in two patients with moderate to severe hepatic dysfunction. This represented 0.2 and 0.4%, respectively, of the administered dose (600 mg, 6-h intravenously in both) excreted in this way. The 24-h biliary volumes were 98 and 160 ml, respectively. The concentration of clindamycin in maxillary bone 4 h after the intramuscular administration of 600 mg of the drug was 0.7 µg/g and 6.5 µg/ml in simultaneously obtained serum samples.

Bacteriology. *S. aureus* was the most common clinical pathogen isolated. All of these isolates and all of the pre-treatment nasal isolates of *S. epidermidis* were inhibited by 0.2 µg or less of clindamycin per ml. One pre-treatment nasal isolate of *S. aureus* was highly resistant to clindamycin (minimal inhibitory concentration, 800 µg/ml). Of the 10 post-treatment nasal isolates, 7 (1 of *S. aureus* and 6 of *S. epidermidis*) were highly resistant (minimal inhibitory concentration, 800 µg/ml) to clindamycin. The resistance of these organisms was not due to a clindamycin-destroying enzyme as evaluated by a modified Haight-Finland test (substituting clindamycin at 0.04 µg/ml in the agar for penicillin). Thus considering all the staphylococcal isolates (clinical and nasal), only 1 of 22 pre-treatment specimens was resistant compared with 7 of 10 post-treatment isolates. This difference was highly significant by Fishers exact test.

From six of the seven patients with paired swabs, *S. epidermidis* was isolated pre- and post-treatment, whereas in the remaining case *S. aureus* was isolated pre-treatment and *S. epidermidis* was isolated post-treatment. Differentiation of the six pairs of *S. epidermidis* was undertaken as outlined in Table 1. With one exception all belonged to biotype 1 of the Baird-Parker classification (1).

All four highly resistant post-treatment isolates showed evidence of resistance to more than one antibiotic. Three of these had clearly different hemolytic patterns from their susceptiole pre-treatment counterparts. The only organisms thought to be identical on the basis of antibiotic susceptibility and hemolytic pattern (pair 5, Table 1) did have the same phage types (157/71A). All other isolates had different phage types.

Adverse reactions. None of the six patients receiving clindamycin intramuscularly complained of local discomfort. Intravenous administration was well tolerated and there was no drug-induced phlebitis. There were no complaints of nausea, vomiting, abdominal pain, or diarrhea. Three patients (7.3%) developed maculopapular eruptions on days 3, 7, and 7 of therapy, respectively. Treatment was continued in one patient with resolution of the rash and no further ill effects. All three patients were receiving other drugs.

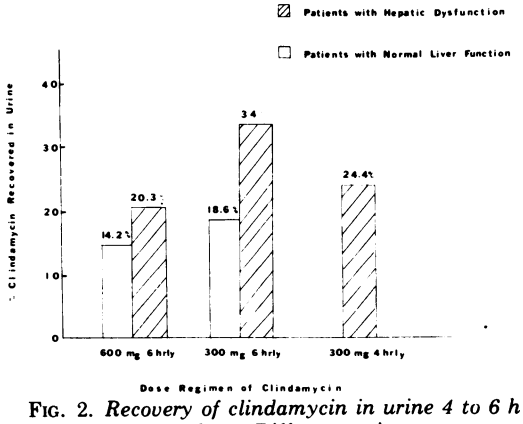

FIG. 2. *Recovery of clindamycin in urine 4 to 6 h after intravenous dose. Differences in percent recovered in patients with and without hepatic dysfunction not significant.*

TABLE 1. *Comparison of six pairs of isolates of S. epidermidis*

Pair no.	MIC[a] to clindamycin (μg/ml)	Antibiogram[b]	Hemolytic pattern with β-toxin-producing *S. aureus*
1. Pre-	000.10	Resistant to tetracycline	Synergistic hemolysis; slight hemolysis alone
Post-	800.00	Resistant to lincomycin, kanamycin, tetracycline, chloramphenicol	Synergistic hemolysis; slight hemolysis alone
2. Pre-	000.05	Susceptible to all	Marked synergistic hemolysis; frankly hemolytic alone
Post-	000.10	Resistant to ampicillin	Synergistic hemolysis; slight hemolysis alone
3. Pre-	000.10	Susceptible to all	Synergistic hemolysis; slight hemolysis alone
Post-	800.00	Resistant to lincomycin, kanamycin, ampicillin, erythromycin, tetracycline	No synergistic hemolysis; slight hemolysis alone
4. Pre-	000.05	Susceptible to all	Marked hemolysis—synergistically and alone
Post-	800.00	Resistant to ampicillin, erythromycin, chloramphenicol, nafcillin	No synergistic hemolysis; no hemolysis alone
5. Pre-	000.05	Resistant to tetracycline, ampicillin	No synergistic hemolysis, no hemolysis alone
Post-	000.10	Resistant to tetracycline, ampicillin	No synergistic hemolysis, no hemolysis alone
6. Pre-	000.10	Resistant to tetracycline, ampicillin	Marked synergistic hemolysis; hemolytic alone
Post-	800.00	Resistant to lincomycin, kanamycin, ampicillin, erythromycin, tetracycline	Synergistic hemolysis; not hemolytic alone

[a] Minimal inhibitory concentration.
[b] Antibiogram: ampicillin, cephalothin, chloramphenicol, erythromycin, kanamycin, lincomycin, nafcillin, and tetracycline disks containing 10, 30, 30, 15, 30, 2, 1, and 30 μg, respectively.

LFTs. Twenty-four patients had evidence of pre-existing hepatic dysfunction, in 19 of whom LFTs taken before, during, and, whenever possible after a course of treatment were available. Further deterioration of liver function occurred in five patients, all of whom were receiving the drug intravenously. All five patients were extremely ill and were receiving a number of other drugs. The major biochemical abnormality was an increase in total bilirubin without significant attendant rise in the hepatic enzyme values. Fractionation of the bilirubin and measurement of the serum haptoglobins revealed no evidence of hemolysis. Three of these patients died; of the remainder one was lost to follow-up, whereas the other slowly improved with return of liver function to normal.

In contrast, five patients with abnormal pre-treatment LFTs showed some improvement during the course of treatment; in three patients, although there was a fall in total bilirubin, there was a modest rise in alkaline phosphatase and one also had an increase in SGOT. In the remaining two patients, both with elevated SGOTs, these values improved.

Four (23.5%) of the 17 patients with normal pre-treatment LFTs, all treated intravenously with clindamycin, showed rises of SGOT. In three of these, transient and reversible rises of SGOT to 52, 57, and 60 mIU/ml were recorded, whereas in the remaining patient, admitted with a drug overdose of barbituates and phenothiazines, an elevated SGOT of 270 mIU/ml was recorded, but it returned to normal 2 weeks after clindamycin therapy was discontinued.

DISCUSSION

At least four clindamycin compounds were present in the various fluids measured: clindamycin phosphate, clindamycin base (hydrochloride), and its two major metabolites, demethyl clindamycin and clindamycin sulfoxide (8; R. M. DeHaan, Upjohn Co., personal communication). The latter three compounds all have antibacterial activity, but no quantitative means of identifying them is known. All samples were measured with a clindamycin base standard so that this potential source of error should be considered here, as in all other studies

of clindamycin pharmacology. The similarity of the mean serum clindamycin concentrations 1 to 2 h, and 5 h, after drug administration in patients with moderate to severe hepatic dysfunction is difficult to explain. It may be due to the persistence of the bacteriologically active clindamycin metabolites in the later serum samples; it is known, for example, that demethyl clindamycin has greater antibacterial activity than the base. In addition, it is possible that conversion of clindamycin phosphate to the base (which occurs rapidly in patients with normal liver function) may be slower in patients with severe liver disease.

The concentrations of clindamycin in serum 5 h after a 600-mg intravenous dose in patients with moderate to severe hepatic dysfunction were significantly higher than those with normal liver function, consistent with the liver being an important site of clindamycin metabolism. There was a positive association between the degree of elevation of the SGOT and the serum level of clindamycin 5 h after an intravenous dose. The serum half-life of clindamycin has previously been shown to be increased two- to fivefold in patients with liver disease (3); we were unable to confirm the view that the prolonged and elevated blood levels lead to an increased frequency of gastrointestinal side effects (3). It is of interest to note that, although there was no statistical difference between the urinary excretion of the drug in patients with and without hepatic dysfunction, there was a twofold greater urinary recovery of clindamycin in those with moderate to severe hepatic dysfunction compared with those with normal liver function. That the urinary route assumes a greater role in excretion of the drug in liver disease is a possibility. The data suggest, however, that both the magnitude of, and the interval between, doses could be modified in patients with liver disease.

Less than 0.5% of the administered dose of clindamycin was recovered in bile from two patients with liver disease. This low recovery may have been due to two factors. First, both patients had severe hepatic dysfunction (bilirubins >3 mg/100 ml; SGOT's >100 mIU/ml). Second, the presence of the T tube in the common bile duct interrupted the enterohepatic circulation of the drug. From these observations it is difficult to make general comments regarding the biliary excretion of clindamycin, although others have indicated that it is a major route of excretion (12).

In keeping with other reported series (4, 8), modest but reversible elevations of serum enzymes occurred during treatment with parenteral clindamycin. In the present series, 4 of 17 patients (23.5%) with normal pre-treatment LFT's showed such enzyme changes. Although the LFT's deteriorated during the treatment of five patients with pre-existing hepatic dysfunction, the complex nature of the illnesses made it impossible to delineate the causative role of clindamycin. In addition, five patients also with pre-existing hepatic dysfunction showed some improvement of liver function during therapy. The data presented do not indicate a hepatotoxic effect.

High-level resistance to clindamycin was found in staphylococci isolated, after day 5 of treatment, from the anterior nares of seven patients. Differentiation of pre- and post-treatment isolates by simple techniques (antibiogram and pattern of synergistic hemolysis) was subsequently confirmed by phage typing. The data suggest that resistant organisms were selected (from the patient or hospital environment) and that clindamycin resistance was not acquired by transduction, transformation, or mutation.

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