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Use of Clindamycin in Patients with Liver Disease

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Hepatotoxicity has been noted by several investigators during parenteral use of clindamycin, and some have reported that drug half-life is prolonged in the presence of liver disease. We administered 300 mg of clindamycin intravenously at 12-h intervals for 2 days to patients with acute and chronic hepatitis, cirrhosis, and controls to determine whether clindamycin will exacerbate preexisting hepatic dysfunction or whether drug excretion will be delayed in patients with liver disease as compared with controls. Exacerbation of hepatotoxicity was not found in this study. There was a small, but significant, delay in drug elimination between cirrhotics and controls, even after the first dose of clindamycin ($P < 0.05$); however, half-lives in all categories were in the range usually considered normal. We conclude that clindamycin can be used in liver disease in some circumstances, if proper precautions are exercised.

Hepatic enzyme elevation has followed parenteral use of clindamycin, and hepatocellular necrosis has been demonstrated after use of the drug (3-5). Clindamycin is excreted primarily in the feces, with 10 to 33% of the administered dose excreted by the kidneys (4, 6). Clindamycin activity in liver abscess cavities has been found to equal serum levels, and drug activity two to five times the serum activity has been found in bile (G. A. Wong, P. D. Hoeprich, L. Effinger, and A. L. Barry, Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 14th, San Francisco, Calif., Abstr. 262, 1974).

This study is an attempt to determine whether clindamycin administered to patients with liver disease will result in exacerbation of liver dysfunction and whether clindamycin dosage adjustments are necessary in the presence of liver disease. We have administered parenteral clindamycin to patients with biopsy-documented liver disease and have observed for the following: (i) exacerbation of existing liver disease or alteration of previously normal hepatic function, (ii) accumulation of drug activity, and (iii) elimination rate of clindamycin in patients with liver disease and normal controls.

MATERIALS AND METHODS

Patient selection. Thirty adults, 22 patients with hepatic diseases admitted to the University of Kansas Medical Center or the Kansas City Veterans Administration Hospital, and 8 normal individuals, physicians, or medical students were studied. Written informed consent was obtained from each individual. Four categories, acute hepatitis, chronic hepatitis, cirrhosis, and controls, were derived according to history, laboratory findings, and liver biopsy results. Biopsies were performed only when clinically indicated and not routinely as part of the study. Each patient continued other necessary medications throughout the course of the study.

Laboratory studies. Serial determinations of hematological, renal, and liver functions were performed during the week before, on day 1 of, and in the week after intravenous administration of clindamycin. These studies included complete blood count, urinalysis, blood urea nitrogen, creatinine, total protein, albumin, serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, and lactic dehydrogenase.

Study groups. (i) Acute hepatitis. Seven patients had acute hepatitis with typical symptoms, including malaise, dark-colored urine, light-colored stools, and icterus. Two of the seven patients had liver biopsy during the illness. The ages ranged from 21 to 39 years, with an average of 28 years. The SGOT was at least twice normal in each patient at the time clindamycin was administered. However, most patients with acute hepatitis were recovering, with decreasing levels of hepatic enzymes during clindamycin administration.

(ii) Chronic hepatitis. Six patients with liver biopsy-confirmed chronic hepatitis showed persistent elevation of the SGOT for at least 6 months. The hepatitis B surface antigen was positive in the serum of four patients with chronic aggressive hepatitis but was negative in the remaining two patients with chronic persistent hepatitis. The average age for the chronic hepatitis group was 32 years, with a range from 22 to 63 years.

(iii) Cirrhosis. Nine patients with cirrhosis had variable hepatic dysfunction and associated chronic alcoholism. The diagnosis of cirrhosis had been con-

firmed by liver biopsy in each patient. The average age was 52 years, ranging from 39 to 71 years.

(iv) **Controls.** The eight medical personnel who served as controls had no known liver disease and normal liver function studies. None of the controls had liver biopsy. Ages ranged from 23 to 29 years, with an average age of 26 years.

Drug administration. Each of the 30 patients received a single, 300-mg intravenous bolus injection of clindamycin-2-phosphate over a 5- to 15-min period. Twenty-eight patients received repeated injections at 12-h intervals for three doses.

Samples. Blood specimens for clindamycin activity were obtained before injection and at 0.5, 1, 2, 4, 6, and 8 h after clindamycin administration on day 1 and after the third dose on day 2. Serum specimens were assayed immediately or were frozen at −70 C when a delay in analysis would occur.

Assay of clindamycin. Serum bioassay for clindamycin activity was performed by the tube dilution method using *Staphylococcus aureus* 209 as the test organism (minimum inhibitory concentration [MIC], 0.078 μg of clindamycin per ml). Serial twofold serum dilutions in 0.5-ml volume were made in brain heart infusion broth in tubes (13 by 100 mm). *S. aureus* 209 in a quantity of 10^4 to 10^5 organisms was added to each tube and was incubated overnight at 37 C. The highest serum dilution showing no visible growth was read as the MIC end point. The MIC for *S. aureus* 209 was redetermined with each assay for serum level. The mathematical product of serum dilution and *S. aureus* 209 MIC resulted in the clindamycin serum activity level in micrograms per milliliter. We prefer the term serum activity of clindamycin because more than one metabolite with bioactivity may be measured by the bioassay.

RESULTS

Clinical studies. Diagnostic categories are shown in Table 1. To be included as chronic hepatitis or cirrhosis, each patient had the diagnosis confirmed by liver biopsy. The mean ages were 28 for acute hepatitis, 33 for chronic hepatitis, 26 for controls, and 52 for cirrhotics. The serum albumin content for cirrhosis was significantly different ($P < 0.05$) from the other categories.

Changes in SGOT and total bilirubin in the week prior to, the day of, and a week after clindamycin administration are shown in Table 2. Liver function was returning toward normal in acute hepatitis and in cirrhosis before clindamycin was given. Despite clindamycin administration, the SGOT and total bilirubin showed continued resolution in each individual of these categories.

Patients with chronic hepatitis, four of whom were hepatitis B surface antigen positive, had increasing SGOT and bilirubin before clindamycin was given. After clindamycin administration, the SGOT and bilirubin improved in all patients, except one, in which there was continuing rise at the time clindamycin was administered. We are unable to exclude the possibility that the continuing elevation in liver function may be related to clindamycin but, because those increases were already occurring when the drug was given, we doubt whether clindamycin was responsible. This patient subsequently had complete resolution of liver function abnormalities.

Serum concentrations. The mean serum clindamycin activity for each group is shown in Table 3. These ranged from 9.7 to 17.4 μg/ml at 0.5 h postinfusion. By 4 h, levels were 1.5 to 6.6 μg/ml and, at 8 h, they were 0.5 to 2.1 μg/ml.

Clindamycin activity levels of cirrhosis compared with controls for 1 h on day 1 were 17 ± 3.1 and 9.7 ± 2.4 ($P < 0.05$); for 8 h, 2.1 ± 0.5 and 0.5 ± 0.1 ($P < 0.01$); and, for 0(12) h on day 2, 1.3 ± 0.2 and 0.1 ± 0.04 ($P < 0.01$). Differences between the controls and acute and chronic hepatitis were not statistically significant (data not shown). Half-lives were obtained by curve fitting with single and double exponential models. Control $T_{1/2}$ was 1.8 h, with 2.6, 2.1, and 2.5 h for acute hepatitis, chronic hepatitis, and cirrhosis, respectively.

DISCUSSION

Clindamycin has been shown effective in a variey of infections. The primary indication for its present use is as an alternative to chloramphenicol in suspected anaerobic infections with *Bacteroides fragilis* (5). Potential usefulness in

TABLE 1. *Categories of patients with liver disease*[a]

Patient category	No. of patients/no. biopsied	Age (yr)		Total protein (g/100 ml)		Albumin (g/100 ml)	
		X̄	SE	X̄	SE	X̄	SE
Acute hepatitis	7/2	28.0	2.6	7.0	0.2	3.7	0.2
Chronic hepatitis	6/6	33.2	7.7	7.0	0.3	3.7	0.2
Cirrhosis	9/9	52.0	4.4	6.9	0.3	2.7	0.02[b]
Control	8/0	25.8	0.6	7.3	0.1	4.4	0.1[b]

[a] X̄, Mean; SE, standard error.
[b] $P < 0.05$.

TABLE 2. *Changes in SGOT and bilirubin in patients receiving clindamycin*[a]

Patient category	SGOT (Karmen units/ml)						Bilirubin (mg/100 ml)					
	Before		During		After		Before		During		After	
	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE
Acute hepatitis	999.6	152.7	778.7	257.6	265.0	116.6	8.5	2.0	6.8	3.3	3.5	1.0
Chronic hepatitis	452.0	230.3	552.8	293.6	454.0	302.6	3.2	1.6	3.6	1.6	4.2	3.4
Cirrhosis	76.0	17.2	65.4	19.2	58.6	11.3	2.7	1.3	2.4	1.3	1.9	0.9
Control			24.6	2.4	21.5	2.0			0.6	0.1	0.6	0.02

[a] $\bar{X}$, Mean; SE, standard error.

TABLE 3. *Mean clindamycin serum activity levels on successive days of administration after 300 mg intravenously every 12 h*[a]

Time (h)	Mean clindamycin serum activity levels (μg/ml)															
	Acute hepatitis				Chronic hepatitis				Cirrhosis				Control			
	Day 1		Day 2		Day 1		Day 2		Day 1		Day 2		Day 1		Day 2	
	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE	$\bar{X}$	SE
0	0	0	0.4	0.04	0	0	0.8	0.3	0	0	1.3	0.2	0	0	0.1	0.04
1/2	15.3	5.2	8.1	4.2	17.4	11.7	32.4	16.4	17	3.1	19.6	2.5	9.7	2.4	12.1	4.4
1	6.0	1.0	7.5	2.3	7.0	2.3	7.8	2.5	13.5	3.2	20.0	7.1	5.3	0.7	6.9	0.9
2	3.3	0.9	3.6	0.3	5.9	1.4	4.4	1.0	10	1.7	10.7	1.4	4.7	0.9	3.6	0.6
4	1.5	0.3	1.8	0.2	2.2	0.5	3.2	0.8	6.6	0.8	6.2	0.7	2.3	0.4	1.8	0.3
6	1.2	0.3	1.7	0.3	1.5	0.4	2.0	0.6	3.4	0.5	4.0	0.9	0.9	0.2	1.0	0.2
8	0.8	0.2	1.2	0.3	0.8	0.2	1.0	0.3	2.1	0.5	2.9	0.8	0.5	0.1	0.6	0.1

[a] $\bar{X}$, Mean; SE standard error.

situations where liver disease coexists is prevalent.

Previous reports have associated the use of clindamycin with the onset of hepatocellular dysfunction (3–5) but, even in reports with biopsy-confirmed hepatocellular necrosis, there has been partial or complete resolution while the drug was being given (3) or shortly after it was stopped. Delineation of the effect of liver disease on the metabolism of clindamycin is important so that therapeutic adjustments may be made if indicated.

Brandl and co-workers reported prolonged half-life (6.4 h) in 10 patients with hepatic abnormalities, as compared with 6 normal controls (3.0 h) (1). A tendency toward clindamycin accumulation was noted with 8-h levels, 2.1 and 1.3 μg/ml, respectively. These studies resulted in the suggestion that clindamycin is contraindicated in patients with severe liver disease.

In contrast, we found that there was a modest 39% increase in clindamycin half-life for cirrhosis, compared with control values ($P < 0.05$). However, these half-life values are within the range usually considered normal (1 to 5 h; median, about 3 h) (2). Similarly G. R. Avant, S. Schenker, and R. H. Alford (Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 14th, San Francisco, Calif., Abstr. 260, 1974) observed a 34% prolongation of half-life from 3.26 to 4.40 h in six patients with cirrhosis. In that study, the trend towards decreased drug elimination was not statistically significant. However, Williams and co-workers (7) have recently shown higher clindamycin activity levels at 5 h in patients with elevated SGOTs, as compared to those with normal liver functions. They noted a positive correlation between the degree of elevation of the SGOT and the serum clindamycin activity level.

Despite our observed differences in half-life values, there was not a significant difference between serum activity levels in acute or chronic hepatitis when compared with controls. Similarly, we found no correlation between the level of SGOT and the 8-h drug activity level. As shown in Table 2, continuing resolution of hepatitis, manifested by declining SGOT, was occurring in both acute hepatitis and cirrhosis patients at the time clindamycin was administered. There were significant elevations in the drug activity levels for cirrhosis versus controls on both days of therapy.

Since the study of Brandl et al. (1) showed a twofold increase (3.0 to 6.4 h) in half-life after a single dose of clindamycin, this protocol was designed to cautiously determine whether rapid accumulation of clindamycin would occur after three doses in patients with liver disease. If drug accumulation did occur in hepatitis or

cirrhosis, we questioned whether further hepatic damage would result. Direct hepatotoxicity is usually dose related, and we have shown that 300 mg of clindamycin given every 12 h does not appear to produce additional hepatitis, nor is there a dramatic tendency for drug accumulation. In the future, we believe it is important to evaluate patients with liver disease and infections for which longer therapy with clindamycin is necessary. From the present work, we would suggest that clindamycin can be used in patients with acute or chronic hepatitis, or cirrhosis, but that periodic observations of drug activity levels and liver enzyme determinations should be made.

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