Cefotetan-Induced Disulfiram-Type Reactions and Hypoprothrombinemia

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A double-blind, placebo-controlled study in eight healthy male volunteers was conducted to study possible disulfiram-type reactions and hypoprothrombinemia associated with cefotetan administration. Three doses of cefotetan (2 g) or of placebo were administered at 12-h intervals. Ethanol (0.5 g/kg of total body weight) was ingested 1 h after the third dose. Blood ethanol, serum acetaldehyde, and prothrombin times were measured throughout the study. Heart rate, blood pressure, and clinical signs as well as symptoms suggestive of a disulfiram-type reaction were also noted. Five of eight volunteers that received cefotetan showed significant flushing. A significant increase in heart rate also was noted. No change in mean arterial pressure was observed during the cefotetan phase, and no one experienced nausea or vomiting. No statistical differences were observed between phases with respect to ethanol area under the time-concentration curve, elimination rate, or serum acetaldehyde concentrations. A slight but statistically significant increase in prothrombin time also was observed with cefotetan. This study suggests that patients receiving cefotetan might be at risk to develop disulfiram-type reactions and hypoprothrombinemia.

Disulfiram-type reactions have been reported in patients who consume alcoholic preparations while receiving ceftaxone (3), cefamandole (S. Drummer, W. E. Hauser, and J. S. Remington, Letter, N. Engl. J. Med. 303:1417–1418, 1980; H. Portier, J. M. Chalopin, M. Freysz, and Y. Tanter, Letter, Lancet ii:263, 1980), cefmenoxime (5), and moxalactam (2; K. R. Brown, B. J. Gugliemo, V. G. Pons, and R. A. Jacobs, Letter, Ann. Intern. Med. 97:621–622, 1982). Disulfiram reactions are due to the inhibition of aldehyde dehydrogenase by disulfiram. This results in the accumulation of acetaldehyde, a metabolite that is produced as a consequence of the ingestion of ethanol (6). Facial flushing, nausea, vomiting, headache, tachycardia, hypotension, or a combination thereof may occur as a result of elevated blood acetaldehyde concentrations (6). The cephalosporins associated with disulfiram-type reactions all have a methylethazolothiol side chain in common (9). This side chain has also been associated with hypoprothrombinemia and bleeding episodes (4, 12, 13). The purpose of this investigation was to determine whether cefotetan, a cephalosporin that contains the methylethazolothiol side chain, exhibits disulfiram-type or hypoprothrombinemic activity.

MATERIALS AND METHODS

A double-blind, placebo-controlled study was performed in eight healthy male volunteers whose subject characteristics are listed in Table 1. Informed consent was obtained from each volunteer. The study was approved by the committee on human research. Subjects were excluded from the study if they reported a history of hypersensitivity to cephalosporins or penicillins, cardiovascular, neurologic, renal, or liver disease, drug dependency, or daily alcohol ingestion. No volunteer was taking any medication, and none had a recent history of receiving cephalosporins or medications reported to cause a disulfiram-type reaction (sulfonamides, chloramphenicol, furazolidone, griseofulvin, quinacrine, chlorpropamide, metronizalole, or tolbutamide) (8).

The study consisted of two phases. During phase 1, subjects were randomly assigned to receive three 50-ml doses of either 0.9% sodium chloride (placebo) or cefotetan (2 g mixed in 0.9% sodium chloride). These doses were infused over 5 min at 12-h intervals. One hour after the third dose, the subjects drank an alcoholic mixture (0.5 g of ethanol per kg of total body weight) over a 15-min period. This mixture was prepared with 80-proof vodka diluted 1:2 with orange juice and served with ice. Before the alcohol consumption, an intravenous line of 0.9% sodium chloride was initiated in each volunteer in the event that a disulfiram-type reaction would lead to a medical emergency. The subjects fasted for 9 h before receiving the alcoholic mixture and for 4 h after its ingestion. They were permitted to drink water freely throughout the study. In addition, they were instructed to abstain from alcohol starting 72 hours before and throughout each study phase. In phase 2, which was conducted 10 days later, the volunteers were crossed over and received the opposite treatment.

Blood pressure and heart rate were measured in the volunteers at each blood collection. A single investigator (S.S.K.) was responsible for questioning and observing all volunteers for the presence of signs or symptoms suggestive of a disulfiram-type reaction. The degree of flushing was ranked on an arbitrary scale of 0 to 3+ (0, no flushing observed; 1+, partial facial flushing; 2+, full facial flushing; 3+, full facial flushing extending to the neck).

During each phase, blood samples (3 ml) for blood ethanol concentration analyses were obtained through a heparin lock into evacuated collection tubes containing potassium oxalate, iced, and later frozen. Blood was collected immediately before and 7, 15, 25, 30, 45, 60, 75, 105, 135, 165, 195, and 225 min after the start of drinking the alcoholic mixture. In addition, blood (7 ml) was collected for an acetaldehyde serum concentration determination in heparinized evacuated collection tubes at 60 min after the alcohol ingestion. This
sample was centrifuged and separated, and the plasma was frozen. Immediately before the first dose of antibiotic or placebo and 5 h after the third dose, blood (3 ml) was collected into evacuated collection tubes containing potassium citrate for prothrombin time determination. Ethanol blood concentrations and acetaldehyde serum concentrations were assayed by gas chromatography. The sensitivity of the ethanol assay is 10 mg/dl, with an intranrun coefficient of variation of 2%. Prothrombin times were measured by the standard one-phase procedure.

**Datum analysis.** Ethanol area under the concentration-time curve from time zero to infinity (AUC<sub>0-∞</sub>) was calculated by the trapezoidal rule. Ethanol is metabolized in the body at a constant rate regardless of serum concentration (zero-order kinetics) (11). Therefore, the ethanol elimination rate was determined by utilizing linear regression analysis of the terminal phase for each subject. Statistical comparison of the mean AUC<sub>0-∞</sub> ethanol elimination rate, heart rate, blood pressure, acetaldehyde serum concentration, and prothrombin time values for the two groups was accomplished by the two-tailed Student t test for paired data. The maximum ethanol concentration and time to maximum ethanol concentration were noted for each subject during each phase. Incidence of disulfiram-type reactions and other adverse effects were statistically analyzed by using the chi-square test. Differences were considered statistically significant if P was <0.05.

**RESULTS**

All subjects successfully completed the study. Mean arterial pressures and heart rates are recorded in Fig. 1. A comparison of the mean arterial pressures between treatment groups showed no significant difference. A transient elevation in mean arterial pressure occurred within 30 min after the consumption of alcohol in both phases of the study. This was followed by a fall in mean arterial pressure which was most prominent 75 min postingestion and, when compared to the baseline, was significant only during the placebo phase. The mean arterial pressure decreased 10 mm Hg or more in three volunteers during the cefotetan phase; however, a similar observation was made during the placebo phase. None of the subjects experienced hypotension that required fluid resuscitation during the study.

The heart rate remained fairly constant among all subjects during the placebo phase. However, during the cefotetan phase, a significant increase in heart rate occurred 45 min after ethanol ingestion (80 ± 4 beats per min) compared with the baseline rate (69 ± 3 beats per min). Overall, the heart rate increased in seven subjects. In four of them, the heart rate increased by 20 beats per min or more from the baseline. None of the subjects experienced hypotension.

The incidence of clinical signs and symptoms suggestive of disulfiram-type reactions during the study was as follows.

None of the volunteers experienced nausea, vomiting, or headache in either phase of the study. However, the incidence of flushing associated with cefotetan use was significantly greater (P < 0.05) than in the placebo group. In the cefotetan group, three subjects experienced 2+ flushing and two subjects experienced 3+ flushing. In the placebo group, none of the volunteers experienced flushing during the control phase. Six volunteers reported diarrhea while receiving cefotetan, one of which experienced diarrhea during the placebo phase. The incidence of diarrhea associated with cefotetan was statistically significant.

The mean blood ethanol concentrations with and without cefotetan are plotted in Fig. 2. Differences in concentrations between the two study phases were statistically insignificant. The ethanol AUC<sub>0-∞</sub> elimination rate, maximum ethanol concentration, time to maximum ethanol concentration, and serum acetaldehyde concentrations for each subject are shown in Table 2. No statistical differences were observed between phases with respect to ethanol AUC<sub>0-∞</sub> and elimination rate. The ethanol AUC<sub>0-∞</sub> during the placebo and cefotetan phases was 124 ± 15 and 137 ± 16 mg · h/dl (mean ± standard error of the mean), respectively. The ethanol elimination rate was 13 mg/dl per h in each phase.

Data for the pre- and postphase prothrombin times were only available for analysis in seven subjects. The use of

<table>
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<th>Subject</th>
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<th>Protocol order*</th>
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<tr>
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* P, Placebo phase; C, cefotetan phase.

FIG. 1. Mean arterial pressures and heart rates with cefotetan and placebo administration. The asterisk indicates a P of <0.05 when compared with the baseline.

FIG. 2. Mean blood ethanol concentrations with cefotetan and placebo administration.
The results of the double-blind randomized trial described in this report suggest that cefotetan, a newly marketed cephalosporin containing the methyltetrathiolethiol side chain, also may produce a disulfiram-type reaction. In this study, subjects received three doses of cefotetan or placebo administered every 12 h on two separate occasions. Five of eight subjects experienced noticeable flushing within 15 to 60 min of ingesting a vodka-orange juice mixture administered 1 h after the third dose of antibiotic. Flushing was not observed during the placebo phase in any of the subjects. None of the subjects suffered nausea, vomiting, or headaches in either phase. The greater incidence of diarrhea during the cefotetan phase was attributed to the alteration in gastrointestinal tract flora by the antibiotic.

In a recently published report, disulfiram-type reactions associated with cephalosporin use, the antibiotic had preceded ethanol ingestion (2, 3, 5; Brown et al., Letter; Drummer et al., Letter; Portier et al., Letter). Therefore, this study did not attempt to investigate whether this reaction would occur if cefotetan was administered after alcohol administration.

Both increases and decreases in blood pressure have been reported after the ingestion of ethanol (1, 10). Our results suggest that any changes in blood pressure in our volunteers were unrelated to cefotetan.

The heart rate in four volunteers, all of whom exhibited 2+ or 3+ flushing, was observed to increase greater than 20 beats per min from the baseline during the cefotetan phase, but not during the placebo phase. Although transient elevations in heart rate have been reported after the ingestion of ethanol, the increase in heart rate in this study appears to be a result of a disulfiram-type reaction during the cefotetan phase, since a similar increase in heart rate was absent during the placebo phase and in volunteers who did not develop flushing (7).

No statistically significant differences were observed in ethanol elimination, blood ethanol concentrations, or ethanol AUC0-1 in subjects treated with cefotetan or placebo. However, there was observed to be a slight increase in blood ethanol concentrations, AUC0-1, and elimination rate. No correlation between ethanol levels or change in ethanol levels with the incidence of disulfiram-type reactions was observed. The patients with the greatest degree of flushing had ethanol AUC0-1s and peak ethanol concentrations of less than the calculated means. The patient with the greatest AUC0-1 was asymptomatic throughout the study. Our results suggest that the presence of a disulfiram-type reaction after the cefotetan is independent of blood ethanol concentrations.

Furthermore, we did not observe any statistically significant changes in serum acetaldehyde concentrations between phases. In fact, some patients who experienced flushing actually had lower acetaldehyde levels during the cefotetan phase. These results suggest that the presence of a disulfiram-type reaction is unrelated to the acetaldehyde concentration.

The clinical implications of a disulfiram-type reaction occurring when ethanol is ingested by a patient receiving cefotetan cannot be ignored. In our trial, patients received an average of 44 g of ethanol, an amount greater than that contained in typical doses of medicinal agents. However, some patients have experienced disulfiram-type reactions when receiving as little as 2 to 20 g of ethanol 24 to 48 h after the administration of a cephalosporin (3; Brown et al., Letter; Portier et al., Letter).

Hypoprothrombinemia has been reported in patients receiving cephalosporins containing the methyltetrathiolethiol side chain, mostly in patients with renal failure or malnutrition (4, 12, 13). In our study, we observed a slight but clinically insignificant increase in prothrombin time from the baseline after three doses of cefotetan. The lack of clinically significant effect of our volunteers is most likely due to the short course of therapy and their excellent health status. However, patients treated with cefotetan should be monitored for possible hypoprothrombinemia, especially if they are at high risk like patients with renal failure or malnutrition.

In summary, eight volunteers consumed ethanol after receiving cefotetan. Five experienced facial flushing, and four exhibited a significant increase in heart rate. None of the volunteers experienced nausea, vomiting, or clinical evidence of a severe disulfiram-type reaction. Likewise, none of them experienced flushing or increased heart rate during the placebo phase. The occurrence of a disulfiram-type reaction was unrelated to the blood ethanol or serum acetaldehyde concentration. A slight increase in prothrombin time was observed with cefotetan but was clinically insignificant. Patients receiving cefotetan are at risk to develop disulfiram-type reactions. Alcohol-containing beverages and medications should be avoided, if possible, in

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**DISCUSSION**

**TABLE 2. Ethanol and acetaldehyde pharmacokinetic parameters during the placebo (P) and cefotetan (C) phases**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Ethanol AUC0-1 (mg·h/dl)</th>
<th>Ethanol elimination rate (mg/dl per h)</th>
<th>Ethanol Cmax (mg/dl)</th>
<th>Ethanol Tmax (min)</th>
<th>Serum acetaldehyde at 60 min (mg/liter)</th>
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<tbody>
<tr>
<td></td>
<td>P</td>
<td>C</td>
<td>P</td>
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<tr>
<td>Mean ± SEM</td>
<td>124 ± 15</td>
<td>137 ± 16</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
<td>62 ± 6</td>
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* --, Data unavailable.
these patients for 48 h or longer after the discontinuation of cefotetan. Additionally, prothrombin times and evidence of clinical bleeding should be monitored in patients with possible vitamin K deficiency.

ACKNOWLEDGMENTS

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LITERATURE CITED