Effect of Diuretics on Urinary Excretion of Cephalothin in Humans

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Diuretics and antibiotics are frequently used concomitantly. The possibility of drug interactions led us to study the effects of several diuretics on the renal elimination of cephalothin. Five healthy volunteers received a constant infusion of 500 mg of sodium cephalothin per h for 9 h on 4 consecutive days. Each day, after the third hour of infusion, the subjects were given one of the following in varying order: (i) furosemide (1 mg/kg, intravenous), (ii) mercaptomerin (250 mg, intramuscular), (iii) mannitol (25 g, intravenous), or (iv) no diuretic (control day). Fluid losses were replaced hourly. Serum and complete urine collections were obtained each hour and assayed for creatinine and cephalothin (bioassay). Clearances (milliliter per minute) and urinary excretions (milligram per hour) of cephalothin did not differ either when the diuretic day values were compared with control day, or when pre- and postdiuretic results on the same day were compared. Creatinine clearances were not affected by diuretics except for a transient rise after furosemide.

Cephalothin, an organic anion, is actively secreted by the proximal tubule of the kidney (7). Evidence has been presented to indicate that active transport of weak organic acids in the rabbit kidney is influenced by the concentration of cations present (3). Because the action of many diuretics involves alterations in the migration of cations, it appeared that the administration of diuretic agents to patients might influence the rate of urinary excretion of cephalothin.

The purpose of the present study was to examine the effects of three diuretics, each with a different mode of action, on the renal excretion of cephalothin.

MATERIALS AND METHODS

Three men and two women, 21 to 29 years of age, volunteered for the study. Their heights and weights varied from 168 to 185 cm and 54 to 87 kg, respectively. Informed consent was obtained from each individual before the study was started. None had ingested alcohol or drugs in the 48 h before entering the study. Physical examinations were normal. Electrocardiogram, chest X ray, urinalysis, complete blood count, prothrombin time, serum creatinine, urea nitrogen, electrolytes, glutamic oxalacetic transaminase, bilirubin, protein, and alkaline phosphatase were within normal limits. Serum electrolytes, creatinine, and urea nitrogen were measured daily.

Subjects were hospitalized the night before the study was started. On each of the succeeding 4 days, they were given cephalothin with (i) no diuretic, (ii) furosemide (Lasix-Hoechst Pharmaceuticals Co., Somerville, N.J.), (iii) mannitol (Abbott Laboratories, Chicago, Ill.) or (iv) mercaptomerin (Thiomerin-Wyeth Laboratories, Philadelphia, Pa.). The sequences in which the diuretics were administered were (ii), (iii), (iv), (i) in one volunteer, (i), (ii), (iii), (iv) in two, and (i), (ii), (i), (iv) in two. The doses were as follows: furosemide, 1 mg/kg intravenously over 2 min; mercaptomerin, 250 mg intramuscularly; mannitol, 25 g (in 100 ml) intravenously over 20 min. The volunteers emptied their bladders as completely as possible at the end of each hour of study, after which venous blood was drawn immediately. In the first 2 h after administration of furosemide and mannitol, specimens were collected at intervals of 90 rather than 60 min. Subjects were not allowed to smoke and remained recumbent throughout the period of infusion except when voiding. To maintain urinary output and a steady state of fluid balance, water or fruit juice was
given each hour in a volume sufficient to replace the
difference between fluid losses (urine and insensible
loss) and the amount infused.

Concentrations of antibiotic in urine and serum
were determined by an agar diffusion method using
Trypticase soy agar (Baltimore Biological Labora-
tories, Baltimore, Md.) seeded with Bacillus subtilis
spores (Difco, Detroit, Mich.) (1). This method of
assay is accurate in our laboratory to ±12% over a
range of concentrations from 1 to 50 μg of cephalothin
per ml. Standards were prepared by dissolving the
antibiotic in serum obtained from each volunteer
before the antibiotic was given. pH of urine was
measured by pHydron paper (Micro Essential Lab-
Brooklyn, N.Y.).

RESULTS

Figure 1 shows the mean concentration of
cephalothin in the serum of five volunteers at
different time intervals during each regimen.
These varied little from hour to hour or day to
day for the same person. However, the variation
among individuals ranged from a mean of 6.8 to
19.1 µg/ml on the control day. There was a
direct correlation between serum levels and
dose administered (6.7 to 9.3) in milligrams per
kilogram per hour by linear regression analysis
(\( P < 0.05 \)).

The mean volumes of urine excreted are
represented by the white bars in Fig. 2. Al-
though there was a large variation in volumes of
urine among volunteers, individual volumes
varied little from hour to hour except after
diuretic administration. On the control day,
there was a progressive rise in urinary output.
On the diuretic days, furosemide produced a
striking early diuresis (1,419 ml/h); mercap-
tomerin produced a later diuresis, and mannitol
produced no significant increase in urine vol-
ume.

The mean amounts of cephalothin excreted
are represented by the black bars in Fig. 2. The
first hour amounts were always highest because
of the initial bolus of cephalothin. Although
there appeared to be a transient increase in the
excretion of antibiotic during the hour after
injection of furosemide, the values were not
significantly different from those of the preced-
ing hour when compared by the Student's paired
t test. Thus, the administration of these diuret-
ics led to no demonstrable change in the rate
of urinary excretion of the antimicrobial agent.
There was no correlation between the volume of
urine and the amount of cephalothin excreted
by an individual during the control day.

The clearances (UV/P adjusted to 1.73 m²
surface area) of creatinine and cephalothin for
furosemide and mercapto merin are indicated in
Fig. 3 and 4. Creatinine clearance was remark-
ably stable from day to day and from hour to
hour, except for a brief but not statistically
significant rise after the injection of furosemide.
Values on the control day ranged from 123 to
166 ml/min (mean and standard error \( 142 \pm 3.8
ml/min \)).

The mean rate of clearance of the antibiotic
for all subjects during hours 2 through 9 of study
on the control day was 498 ± 23 ml/min. Values
varied considerably among individuals, but
The mean urinary pH on the control day was 6.2 with little difference among individuals or at different hours. Furosemide and mercaptomerin produced a decrease in pH to 5.1 and 5.3, respectively, shortly after maximal diuresis, whereas mannitol produced no change.

None of the volunteers experienced any adverse symptoms during the study.

**DISCUSSION**

Cephalothin and its metabolites are eliminated for the most part by renal mechanisms. Like the penicillins, this antibiotic is both filtered by the glomerulus and actively secreted by the proximal renal tubule. The maximum tubular secretory capacity for this agent in man is not known. A small amount of cephalothin may be reabsorbed in the nephron, particularly when the urine is very acidic (17). In the present study, the clearance of cephalothin at serum levels of 6 to 20 μg/ml was noted to be three to five times greater than that of creatinine. The fraction of cephalothin which is protein bound in human serum, hence not filtered at the glomerulus, is approximately 65% (10). Thus, the rate of clearance of the antibiotic attributable to glomerular filtration alone would be creatinine clearance (142 ml/min) times the portion unbound (35% or 49.7 ml/min) based on the data from the control day. The observed clearance of cephalothin of 498 ml/min exceeds this by ninefold, emphasizing the prodigious role of tubular secretion in the elimination of the antibiotic in these individuals. These values for the clearance of the drug are higher than those reported by others (10, 14).

The mechanism of diuretic action of furosemide has been attributed to its inhibition of reabsorption of water and electrolytes in the loop of Henle and possibly the proximal and distal tubule action as well (6). In addition, renal blood flow and glomerular filtration may be augmented by this agent. These factors may have been responsible for the transient increase in creatinine clearance which was observed after the injection of furosemide (15). A similar phenomenon has been described by others (13). Mannitol causes a diuresis by osmotic retardation of the reabsorption of tubular fluid (7). Mercaptomerin’s main site of action remains controversial but can probably be localized in the loop of Henle (8).

Although none of the diuretics studied would be expected to affect the rate of filtration of cephalothin, there were several reasons to suspect the possibility of an interaction at the sites of active tubular transport. Furosemide has
been shown to compete with probenecid for secretion by the proximal renal tubule (9) and to increase clearance of para-aminohippuric acid (5). Mercaptomerin appears to interfere with the active transport of para-aminohippuric acid (11, 16), although its own secretion is not affected by probenecid (2). The transport of these organic acids as well as of most penicillins and cephalosporins is thought to involve a limited number of pathways, so that interactions among them would not be surprising (12). Moreover, all three diuretics alter the migration of inorganic cations which are essential for the transport of weak organic acids at various sites including the intestinal mucosa (4) and kidney (3).

No significant effect of any of the diuretics on the renal clearance of cephalothin was detected in the present study. Although this suggests that there is no important interaction among these agents at ordinary therapeutic concentrations, the extent of diuresis achieved with mannitol was small, and larger doses might have produced different results. The study was designed to produce and maintain a mildly positive fluid balance throughout the infusion of antibiotic to insure that the hourly collections of urine would be reasonably complete and that volume depletion would not occur. However, during the first 3 h of the furosemide trial and throughout the control day, the volumes of urine excreted were greater than had been anticipated. The particularly high rates of urinary flow observed during the control day may possibly be related to the order of administration of the diuretics since this regimen was the first administered to four of the five volunteers. Because there was no correlation between the volume of urine produced by an individual and the amount of cephalothin excreted, it is unlikely that the positive fluid balance during the baseline periods and the control day had an important effect on the results.

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LITERATURE CITED


