Pharmacokinetics of Cefoperazone and Tobramycin Alone and in Combination

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Certain beta-lactams have been shown to increase the clearance of tobramycin. We evaluated the pharmacokinetics of cefoperazone and tobramycin, alone and in combination, in healthy volunteers. No significant alteration in pharmacokinetic behavior was noted for cefoperazone or tobramycin alone or in combination.

The treatment of serious pseudomonal infections often requires the use of beta-lactams in combination with aminoglycosides (3). Although this combination is well established in therapy (8), it is known that the antipseudomonal penicillins can interact with aminoglycosides both in vitro and in vivo to form a microbiologically inactive compound. This effect appears to be time, concentration, and temperature related (9) and is particularly relevant in those patients with decreased glomerular filtration rates (4). Cephalosporins appear to interact minimally with aminoglycosides in this manner. However, moxalactam has been observed to interact in vivo with tobramycin when given in combination (1). Unlike the previous interactions with beta-lactams and aminoglycosides, no in vitro interaction was noted. Tobramycin clearance increased when it was administered along with moxalactam to normal volunteers and to patients with renal failure. Conversely, moxalactam clearance decreased when tobramycin was given at the same time to volunteers with normal renal function.

In this study, we investigated the pharmacokinetic behavior of cefoperazone and tobramycin alone and in combination. Cefoperazone and tobramycin were studied because of their known potent antipseudomonal activity (7) and their likelihood of being used in combination in serious pseudomonal infection.

MATERIALS AND METHODS

Volunteers. Eight healthy test subjects (four males and four females) with no known allergies to penicillin or other beta-lactam agents participated in the study. Informed written consent was obtained from all volunteers. The study was approved by the Committee on Human Research of the University of California. None of the females was known to be pregnant, and none of the volunteers took other antimicrobial agents, probenecid, aspirin, or other inhibitors of active tubular secretion during the 2 weeks preceding the study. No caffeine or alcohol was taken on the study days. The mean age of the subjects was 25 years (range, 23 to 28 years), and the mean weight was 66 kg (range, 49 to 88 kg).

Dosage. After an overnight fast, the subjects were dosed randomly with 30 mg of cefoperazone per kg, 1.5 mg of tobramycin per kg, or a combination of cefoperazone and tobramycin. After a 1-week washout period, the subjects were crossed over to the second regimen. A subsequent 1-week washout period was followed by the third antibiotic regimen. The antibiotics were administered separately in 50 ml of a 5% glucose solution over 25 min via a peripheral vein access by using a constant-rate Harvard infusion pump. After infusion of the antibiotic(s), the intravenous lines were flushed with normal saline to ensure complete delivery of the antibiotic.

Sampling. Blood samples for assay of antibiotic concentrations in serum were drawn before administration and at 0.42, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the start of the infusion. The samples were immediately placed on ice, centrifuged, and then stored at −20°C until assayed. Urine samples were collected before administration of the dose and from 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 8, 8 to 12, and 12 to 24 h after administration. No detectable antibiotic was observed in the blood or urine samples collected before drug administration.

Antibiotic assay. Cefoperazone concentrations in serum and urine samples were determined in our laboratory by high-pressure liquid chromatography. For concentrations in serum samples, a reverse-phase C-18 Alltech column was used in conjunction with a mobile phase of 30% acetonitrile, 0.1% phosphoric acid, and 0.03% tetramethylammonium chloride. Spectrophotometric determinations were made at 254 nm with a Waters 441 detector. Ticarcillin was used as the internal standard.

For determination of cefoperazone concentrations in urine samples, the same column and detectors were used; however, the mobile phase consisted of 20% acetonitrile, 0.1% phosphoric acid, and 0.05% tetramethylammonium chloride. Furazolidone was used as the internal standard. Reproducibility measurements yielded intraday and interday variability of less than 7.5%. The lowest assayable concentrations in plasma and urine were 0.5 and 1.0 μg/ml, respectively.

Concentrations of tobramycin in serum samples were determined by using a specific fluorescence polarization immunoassay (TDX; Abbott Laboratories, Irving, Tex.). Reproducibility measurements yielded intraday and interday variability of <4%. The limit of detection was 0.18 μg/ml.
Pharmacokinetic analysis. Serum concentration-time profiles were fitted to a one-compartment open model with zero-order input and also by noncompartmental methods (5, 6). Curve fitting was used primarily for estimation of the terminal elimination rate constant and half-life. The area under the serum concentration-time curve (AUC) was calculated by the log-trapezoidal rule with extrapolation to infinity. Total body clearance was derived by dividing the antibiotic dose by the AUC. The volume of distribution at steady state ($V_{ss}$) was calculated by using the following equation: $V_{ss} = \text{dose}[(\text{AUMC})/(\text{AUC})^2] - t'\text{(dose)}(2/(\text{AUC}))$ where $t'$ is the infusion duration time and AUMC is the area under the first moment curve measured by the log-trapezoidal rule. Renal clearance of cefoperazone was determined by dividing the amount excreted in the urine by the AUC for a given collection interval.

Statistical analysis. Statistical analysis was performed using the Student t test on paired data and the Mann-Whitney rank sign test on the PROPHET Computer Resource. Significance for both tests was defined as $P < 0.05$ (2).

RESULTS AND DISCUSSION

The mean serum-concentration-versus-time profiles for cefoperazone alone and in combination with tobramycin are shown in Fig. 1. The mean serum clearance of cefoperazone alone was $87.6 \pm 31.8$ ml/min compared with $73.9 \pm 21.0$ ml/min for the combination. Renal clearance of cefoperazone alone averaged $23.2 \pm 8.0$ ml/min as opposed to $24.9 \pm 7.7$ ml/min in combination. Mean half-lives in sera were $113.9 \pm 26.6$ min and $122.7 \pm 11.1$ min for cefoperazone alone and in combination, respectively. The mean volumes of distribution at steady state were $10.4 \pm 0.5$ liters and $9.4 \pm 3.6$ liters for cefoperazone alone and with tobramycin, respectively. None of the above differences was statistically significant.

The mean serum-concentration-versus-time profiles for tobramycin alone and in combination with cefoperazone are shown in Fig. 2. The mean serum clearance of tobramycin was $86.5 \pm 15.2$ ml/min, and the clearance in combination with cefoperazone was $83.0 \pm 13.7$ ml/min. The mean half-lives in sera were $122 \pm 20.4$ min and $132.9 \pm 42.6$ min for tobramycin alone and in combination, respectively. The mean volumes of distribution at steady state were $13.3 \pm 2.9$ liters for tobramycin alone and $13.0 \pm 2.5$ liters for tobramycin in combination. None of the above pharmacokinetic parameters was significantly different for tobramycin alone compared with the combination.

Unlike moxalactam, cefoperazone, when given in combination with tobramycin, did not alter the pharmacokinetic disposition of the aminoglycoside. Neither did tobramycin significantly affect the kinetic behavior of cefoperazone. Therefore, altered pharmacologic activity secondary to decreased or increased concentrations of either drug in serum is unlikely based on these observations.

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LITERATURE CITED


6. Hoford, N. H. G. 1982. DRUGMODEL, a program for estimating parameters of standard pharmacokinetic models in...

