Bioavailability of Bacampicillin and Talampicillin, Two Oral Prodrugs of Ampicillin

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A 200-mg amount of bacampicillin showed a significantly higher relative extent of bioavailability than did a 250-mg amount of talampicillin, possibly due to their different stability in the digestive juices.

The prodrug technique is increasingly recognized as an approach to obtaining maximum systemic concentrations in the body by the oral route (2). Several prodrugs of ampicillin, such as bacampicillin, pivampicillin, and talampicillin, have been made. The pharmacokinetics of bacampicillin and pivampicillin were compared in a previous report (8). The purpose of the present study was to compare the bioavailabilities of bacampicillin and talampicillin.

The study was conducted in 10 male volunteers, 22 to 41 (mean 31) years old, with body weights ranging from 64 to 91 (mean 76) kg. All were healthy, as evidenced by routine clinical and laboratory examinations, and without known allergy to penicillins or cephalosporins. Before and after study, tests relevant to the renal and liver function, as well as hematological findings, were within normal ranges. Each subject received either a 200-mg (batch F162) or a 400-mg (batch F199) dose of bacampicillin hydrochloride (Penglobe; Astra Läkemedel AB, Sweden) or a 250-mg dose (batch 3902/A) of talampicillin hydrochloride (Talpen; Beecham Research Laboratories, England) in randomized order according to a complete crossover design with 1 week between experiments. After an overnight fast, the drugs were administered under supervision as single doses with 100 ml of water. Food was withheld for 3 h after medication. Intake of water was permitted ad libitum, except during the last hour before and the first hour after medication. The volunteers were instructed not to take any other drugs during the study. The study was approved by a peer review committee, and written informed consent was obtained.

Blood samples were drawn from an antecubital vein before drug intake and 20 and 40 min, 1, 1.5, 2, 4, 6, and 8 h postmedication. Urine was collected at 2-h intervals during 8 h. All samples were stored at −20°C until analyzed. The ampicillin concentrations were determined by the cylinder-plate method, with Micrococcus luteus as test species (7). The detection limit in serum was 0.03 mg/liter. The relative extent of bioavailability was estimated by comparing the areas under the serum concentration versus time curves (AUC), calculated by the trapezoidal rule. A 200-mg amount of bacampicillin was used as standard in each subject. Areas were corrected for dose differences, calculated as anhydrous ampicillin. To test for significant differences in pharmacokinetic variables between drugs and doses (at the 5% level), the nonparametric Friedman analysis of variance was applied, followed by multiple comparisons based on the Friedman rank sums (3).

None of the preadministration samples showed antibacterial activity. Both drugs were rapidly absorbed. The median time from tablet administration to the occurrence of the peak serum level was the same for all three doses, 40 min. The curves after 200 mg of bacampicillin and 250 mg of talampicillin were almost overlapping (Fig. 1). The mean (± standard deviation) individual peak serum concentration of ampicillin was almost the same after 200 mg of bacampicillin (4.2 ± 0.95 mg/liter) and 250 mg of talampicillin (4.0 ± 0.79 mg/liter). An approximately 50% increase in peak concentration was reached when doubling the dose of bacampicillin (6.2 ± 1.28 mg/liter). The individual variation, as expressed by the coefficient of variation, was similar for all three formulations, i.e., 23% (200 mg of bacampicillin), 21% (400 mg of bacampicillin), and 20% (250 mg of talampicillin).

The mean recovery in urine of ampicillin was somewhat lower after talampicillin than after bacampicillin. The differences were, however, not statistically significant (Fig. 1). The mean (± standard error of the mean) relative extent of bioavailability based on AUC comparisons was significantly higher after 200 mg of bacampicillin than it was after either 400 mg of bacampicillin (0.82 ± 0.04; P = 0.01) or talampicillin (0.78 ±
0.03; P < 0.01).

One subject had diarrhea after 400 mg of bacampicillin. The clinical chemistry gave no indications of any effect on liver or kidney function during or after the study.

Although the ampicillin content of a 250-mg dose of talampicillin was 20% higher than that of a 200-mg dose of bacampicillin, these prodrugs produced almost overlapping serum curves. The mean relative extent of bioavailability, based on comparisons of both AUCs and urinary excretion indicates that talampicillin is less well absorbed. This could be explained by different stability in the digestive juices. The rate of nonenzymatic hydrolysis in phosphate buffer (pH 7.4) and synthetic gastric juice (pH 1.2) (USP XVIII) is 5- to 10-fold higher for talampicillin than for bacampicillin (1). The differences might also be due to formulation factors. This aspect was not examined in the present study.

The serum concentrations found in this study are, in general, compatible with previous reports (4–8). The coefficient of variation in individual peak serum concentrations of approximately 20% after all doses is in agreement with previous results with bacampicillin (7, 8), pivampicillin (8), and talampicillin (9), verifying a uniform and reliable absorption of these prodrugs.

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LITERATURE CITED