Absorption of Pivampicillin in Postoperative Patients

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The absorption of orally administered pivampicillin was studied in nine postoperative patients and compared with that of intravenously administered ampicillin. The absorption of pivampicillin was calculated on the basis of comparison of the areas under the serum concentration curves for both modes of administration. After an oral dose of 700 mg the absorption ranged from 40 to 95% (mean, 60%).

Despite its relatively good acid stability, ampicillin is absorbed rather poorly from the gastrointestinal tract, varying from 30 to 50% (8, 10, 12). One of the attempts to achieve better absorption resulted in the development of pivampicillin, the pivaloyloxymethyl ester of ampicillin, which is rapidly hydrolyzed to ampicillin in the body; 15 min after administration, more than 99% of the drug in the blood is present as ampicillin (18).

The serum concentrations of ampicillin after oral administration of pivampicillin have been compared with those after ampicillin given by the oral route (1, 4, 6, 12, 15-17, 19, 20) or intramuscularly (3, 7, 13); only three of these studies were done in patients (6, 12, 13). The general impression obtained from these studies is that after equimolar doses the mean (peak) serum levels of ampicillin after orally administered pivampicillin are two to three times higher than those seen after orally administered ampicillin and are almost comparable with those after intramuscularly administered ampicillin.

Several objections can be raised to most of these studies, however. (i) The amount of the drug absorbed in relation to the dose is difficult to evaluate. (ii) Most of the studies were done in healthy subjects. (iii) The individual variations in absorption, which are important in relation to therapy, were not taken sufficiently into consideration.

A more recent study on the absorption of pivampicillin (10) gives better information about the amount of pivampicillin that is absorbed, but this investigation too was done in healthy subjects.

In the present study the quantitative absorption of oral pivampicillin was compared with that of intravenously administered ampicillin in postoperative patients.

MATERIALS AND METHODS

The investigation was performed in nine adult patients (one female and eight males) aged between 22 and 85 years who had undergone a urological operation recently (within 3 to 7 days). The gastrointestinal function had recovered to the extent that the patients were able to eat normally, and most of them were in the initial phase of postoperative mobilization. Administration of antibiotics was stopped at least 12 h before the study was started. Patients with an allergy to penicillin or (severe) renal failure (serum creatinine more than 250 μmol/liter) were not included. All patients consented to participate in the study after the purpose had been explained.

On day 1, 500 mg of ampicillin (Amfipen; Mycofarm, Delft, The Netherlands) was administered intravenously. Blood samples were taken just before and 2, 5, 15, 30, 45, 60, 75, 90, 105 (from two patients only), 120, and 180 min after the drug was given. On day 2, two 350-mg capsules of pivampicillin, (Pivatil; kindly supplied by Merck, Sharp & Dohme, The Netherlands), equimolar with 2 × 250 mg of ampicillin, were given in about 180 ml of yogurt or milk. Blood samples were taken just before and 15, 30, (45), 60, 90, 120, 180, 240, (330), and 360 min after administration of the drug.

Each 4-ml blood sample, collected via a heparinized intravenous needle, was immediately centrifuged. The serum concentrations were determined on the same day, or the serum was stored at −20 °C until the bioassay was performed (within 7 days).

Ampicillin concentrations in the sera were measured by the agar plate diffusion method of Grove and Randall (5) as modified by Mattie et al. (14), with Bacillus subtilis ATCC 6633 as test organism.

Serum creatinine levels were determined on days 1 and 2, and when pivampicillin administration was continued the levels of bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and lactic dehydrogenase were determined on days 1, 8, and 15, since there have been reports about possible hepatotoxicity in animals. The patients were asked about nausea and upper abdominal discomfort.
RESULTS

The serum concentrations after intravenous administration of 500 mg of ampicillin are shown in Table 1 and those after oral administration of 700 mg of pivampicillin in Table 2 and Fig. 1. From the serum concentrations after intravenous administration the best-fitting curve for a two-compartment open model (21) was calculated. This serum concentration curve can be described as bi-exponential, with the general form:

\[ C_t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]  

(i)

in which \( C_t \) is the serum concentration at time \( t \), and \( A, \alpha, B, \) and \( \beta \) are derived from the pharmacokinetic parameters. The pharmacokinetic parameters were calculated directly by a computer program. The data are shown in Table 3.

The total absorption of pivampicillin was calculated by comparing the areas under the serum concentration curves after intravenous administration of ampicillin and oral administration of pivampicillin. The area under the intravenous curve was calculated with the equation:

\[ \text{area} = A/\alpha + B/\beta \]  

(ii)

The area under the oral curve was determined by the trapezoid method with extrapolation after the last serum concentration \( C_t \) by adding \( C_t/\beta \).

The resulting values of the amount absorbed, expressed as percentage of the administered dose, varied from 40 to 95% (mean, 60%). Calculation of the cumulative absorption after

![Figure 1](http://aac.asm.org/content/21/9/1223/F1.large.jpg)

**Figure 1.** Serum concentrations of ampicillin after oral administration of 700 mg of pivampicillin in nine postoperative patients.

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<th>Table 1. Serum concentrations after intravenous administration of 500 mg of ampicillin</th>
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* Time (minutes) after administration.

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<th>Table 2. Serum concentrations of ampicillin after oral administration of 700 mg of pivampicillin</th>
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* Time (minutes) after administration.
oral administration according to Loo and Riegelman (11) led to somewhat bizarre results, presumably because of the relatively infrequent sampling during the initial phase of absorption. Moreover, values of $k$ $Cl_{1,2}$ varied widely between individuals, suggesting that these values could not be calculated very accurately. Therefore, the cumulative absorption was determined by the one-compartment open model (21) with the equation:

$$D_t/V = C_t + \beta I_0 C dt$$

in which $D_t$ is the total dose absorbed at time $t$ and $V$ is the total volume of distribution ($V_1 + V_2$). Figure 2 shows the results graphically, with the cumulative absorption varying from 200 to 476 mg.

During pivampicillin medication the liver function tests remained within normal limits. Four patients received the drug for only a few days, the others up to 3 weeks. Three patients complained of nausea, two of them only after taking the capsules on an empty stomach; in one case the drug was discontinued because of pain in the upper abdomen.

**DISCUSSION**

In previous studies comparison of orally administered pivampicillin with intramuscularly administered ampicillin (in healthy subjects) suggested that absorption of pivampicillin is nearly complete (3, 7, 10). However, because incomplete absorption of ampicillin after intramuscular administration has been reported (2), the only method of drug administration certain to give 100% absorption of the dose is intravenous administration. Consequently, we chose intravenously administered ampicillin for purpose of comparison in our study.

We assumed that the distribution profile of pivampicillin is identical to that of ampicillin, because 15 min after administration more than 99% of the drug in the blood is already present as ampicillin. The study was performed on two consecutive days, shortly after surgery, since we wanted to study the absorption in the early postoperative phase, with the patient’s condition (bowel motility, mobilization) as identical as possible on both days. When pivampicillin was given there was no detectable ampicillin left in the blood. Unfortunately, since it has proved to be impossible to obtain reliable samples in this kind of patient, we could not measure the urinary recovery of the drugs reliably. We preferred to administer the drug under nonfasting conditions, because pivampicillin is badly tolerated on an empty stomach (1), and food does not seem to impair the absorption of the drug in healthy subjects (3, 7, 16).

In this study the mean absorbed amount of orally administered pivampicillin in postoperative urological patients was 60% of the administered dose. This absorption is better than that of orally administered ampicillin in healthy subjects, but is still far from complete. Furthermore, there were considerable individual variations.

It is also quite possible that the absorption of oral antibiotics is lower in patients than in healthy subjects, but since most of the reported pharmacokinetic studies were done in healthy individuals, only a few data are available for comparison. Hultberg (6) found no difference in

![Fig. 2. Cumulative absorption of pivampicillin after oral administration of 700 mg in nine postoperative patients, calculated from serum concentrations.](http://aac.asm.org/)

**ABSORPTION OF PIVAMPICILLIN**
the absorption of pivampicillin in his patients, most of whom had respiratory tract infection, during acute illness and convalescence. Lund et al. (12), who studied the ampicillin levels in patients after cholecystectomy, found that peak levels after oral administration of pivampicillin occurred earlier and were about four times higher than after oral ampicillin. However, since absolute values of absorption were not given it is not clear whether or not these data are in conflict with ours.

In conclusion, in postoperative, partially mobilized patients the absorption of oral pivampicillin proved to be lower than expected and furthermore varied considerably.

ACKNOWLEDGMENTS

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LITERATURE CITED