Effect of Probenecid on the Apparent Volume of Distribution and Elimination of Cloxacillin

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According to Gibaldi et al. (1968, 1970), the higher serum concentrations of penicillins and cephaloridine reached after administration of probenecid are due not only to slower renal elimination but also to an altered distribution in the body. To determine whether probenecid has a direct effect on the distribution of cloxacillin, the elimination and distribution of cloxacillin was studied in six patients, five lacking kidney function and one with a partially impaired renal function, in the presence or absence of probenecid. No significant difference was found between the mean values of the volume of distribution of cloxacillin with and without probenecid (13.0 and 12.6 liters, respectively). Thus, the hypothesis of Gibaldi et al. could not be confirmed for cloxacillin in patients lacking kidney function. In spite of the absence of kidney function, the value of the elimination rate constant was significantly decreased in the presence of probenecid (from 0.326 to 0.263/h). This might be explained by a blockade by probenecid of the elimination of cloxacillin by the liver.

According to most authors (1, 2, 11), probenecid acts by inhibiting tubular transport of organic acids in the kidney. The elevated serum concentrations of penicillin occurring after administration of probenecid were therefore attributed to inhibition of tubular secretion.

However, in 1968 Gibaldi and Schwartz (5) stated that probenecid leads not only to a decrease in renal elimination but also to a reduction of the apparent volume of distribution of a number of penicillins and cephaloridine in a one-compartment model, and both mechanisms were thought to be responsible for the higher serum concentrations observed during probenecid administration. The authors did not use data of their own, and it may be argued that some of the published data of others that they used were not really suitable for the kind of calculations required to prove their point.

In 1970 Gibaldi et al. published a study (4) on a two-compartment model, using pharmacokinetic parameters obtained in five patients receiving benzylpenicillin by the intravenous route. Their results led them to conclude that the ratio between the amounts of drug in the central and peripheral compartments was changed by probenecid in favor of the central compartment. The only explanation they offered for this phenomenon was a possible interference of probenecid with the penetration of benzylpenicillin into certain body compartments.

Because in our opinion the results obtained by Gibaldi et al. did not warrant their discouragement of the use of probenecid together with penicillin, we investigated the specific claim that probenecid would directly influence the volume of distribution of penicillin. For this purpose we chose patients lacking kidney function, because under this condition an indirect effect on the apparent volume of distribution by probenecid via a reduced elimination is excluded. The penicillin chosen was cloxacillin, because we were familiar with the pharmacokinetics of this drug in patients without renal function (9).

MATERIALS AND METHODS

Patients. Five patients (aged 16 to 29 years) on chronic intermittent hemodialysis and one patient (65 years old) with a moderately diminished renal function (creatinine clearance, 24 ml/min) were included in this investigation. The study was carried out between hemodialysis periods with the patients lying in bed. All five hemodialysis patients had undergone a bilateral nephrectomy. Liver function tests were normal, and none of the patients had an abnormal body temperature.

Cloxacillin assay. Cloxacillin concentrations in the serum were measured by the agar plate diffusion method on phosphate peptone agar (pH 6.5) with Sarcina lutea ATCC 9341, according to Grove and Randall (6) with the modification of Mattie et al. (8). The minimal serum concentration that could be assessed accurately was about 2.5 μg/ml. After collection, all samples were stored at −20 C.
tions were performed within a week.

Administration of cloxacillin. After a loading dose of 1 g, cloxacillin (1 g of sodium salt [Orbenin] in vials for parenteral use) was administered to four of the patients by continuous infusion (Fig. 1). In three of these patients, who were on hemodialysis, cloxacillin was infused at a rate of 0.6 g/h for 4 h. For the fourth patient, the only one with a partially disturbed kidney function, the cloxacillin was infused at a rate of 1.2 g/h during 3 h. In the other two patients, continuous infusion was not possible for practical reasons, and cloxacillin was therefore administered by a single intravenous injection of 1 g. The same procedure was repeated during administration of probenecid.

Administration of probenecid. The dose of probenecid was not adjusted because this drug is mainly eliminated extrarenally (1, 2). Administration of 0.5 g orally at 8-h intervals was started 24 h before the cloxacillin was given.

Calculations: elimination rate. The elimination rate constant of cloxacillin was calculated from the exponentially declining part of the serum concentration curve after termination of the continuous infusion, or from the values obtained 1 h after administration of an intravenous dose.

Apparent volume of distribution. For the one-compartment model, the apparent volume of distribution (V) was calculated by dividing the single intravenous dose (D) by the value of the virtual concentration at time zero (C₀). The latter value is obtained by extrapolation of the exponentially declining part of the serum concentration curve to time zero:

\[
V = \frac{D}{C_0}
\]  

The apparent volume of distribution of cloxacillin during the continuous infusion can be calculated with the following equation (10):

\[
\frac{A_t}{V} = C_t + K \cdot \int_{t_0}^{t} C \cdot dt
\]

in which \(A_t\) is the amount administered up to time \(t\), \(V\) is the apparent volume of distribution, \(C_t\) is the concentration at time \(t\), \(K\) is the elimination rate constant, and \(\int_{t_0}^{t} C \cdot dt\) is the area under the serum concentration curve from time zero to time \(t\). A linear relationship exists between \(A_t\) and the right-hand part of the equation; the slope is equal to \(V\).

RESULTS

Table 1 shows the calculated values of the apparent volume of distribution (V) of cloxacillin, given without or together with probenecid.

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<th>Subject</th>
<th>Sex</th>
<th>V (liter)</th>
<th>Body wt (kg)</th>
<th>(K_{elim}) (h⁻¹)</th>
<th>Administration</th>
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| V       | M   | 15.7     | 15.8        | 58            | 0.278         | 0.236 | Infusion
| G       | M   | 13.1     | 13.3        | 58            | 0.390         | 0.322 | Infusion
| B       | M   | 12.2     | 13.2        | 63            | 0.330         | 0.280 | Infusion
| W       | F   | 10.1     | 9.8         | 64            | 0.358         | 0.319 | One dose
| G1      | F   | 8.8      | 10.8        | 50            | 0.275         | 0.156 | One dose
| Mean    |     | 12.6     | 13.0        | 69            | 0.543         | 0.363 | Countinuous infusion

\(a\) The first five patients were on chronic intermittent hemodialysis; the sixth had a creatinin clearance of 24 ml/min.
\(b\) V, Volume of distribution.
\(c\) \(K_{elim}\), Exponential elimination rate constant.
\(d\) Continuous intravenous infusion.
\(e\) Single intravenous injection.
For each individual patient, the apparent volume of distribution was almost the same under both circumstances. The mean values under the two conditions (12.6 and 13.0 liters, respectively) did not differ significantly (0.30 < \( P < 0.40 \)). The relative volume of distribution without and with probenecid was 20.4 and 21.7% of the body weight, respectively.

Despite the total absence of kidney function, the values of the elimination rate constant for the hemodialysis patient differed significantly under the two conditions: probenecid diminished the elimination rate constant from 0.326 to 0.263/h, corresponding to a prolongation of the half-life from 2 h and 8 min to 2 h and 38 min.

The mean value for the elimination rate constant of cloxacillin in anuric patients (0.326/h) is in close accordance with the value we obtained in anuric patients after a single intravenous injection (9). Tables 2 to 4 give the serum concentrations in each individual patient.

**DISCUSSION**

From the results of our study, we conclude that probenecid does not significantly change the apparent volume of distribution for cloxacillin in a one-compartment model in anuric patients. In this respect there seems to be no difference between continuous administration and a single injection.

This finding does not exclude the possibility that probenecid can bring about an increase in the ratio between the concentrations in the central and the peripheral compartments. However, in our opinion such a shift would be expressed in a reduction of the calculated apparent volume of distribution in the one-compartment model.

If a change in the concentration ratio after a single dose can indeed be calculated for individuals with a normal kidney function, such a shift must be an indirect effect of probenecid, because the slower elimination will lead to a smaller difference between the concentrations in the central and peripheral compartments.

Because the administration of probenecid to healthy subjects leads in any case to higher

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<td>Serum conc (( \mu )g/ml) after:</td>
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* Infusion lasted for first 4 h.
* Time, 7.17 h.
* Time, 8.83 h.

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serum concentrations, there is no reason to assume that the concentration in the tissues is not also higher in probenecid-treated patients. Therefore, there is no reason to suppose that under the influence of probenecid a lower concentration of a penicillin will exist at the site of an infection.

In our opinion, probenecid can be used safely and with profit in patients who need high concentrations of a penicillin.

It is also interesting that, in spite of the complete absence of kidney function, anuric patients show a significant reduction of the elimination. It is evident that probenecid diminishes not only the renal but also the extrarenal elimination. This phenomenon can possibly be explained by a blockade of the elimination by the liver. This possibility is supported by Fishman's (3) observation that probenecid reduces the ratio of the liver-to-serum concentration of benzylpenicillin in nephrectomized dogs. The uptake of other drugs by the liver, including rifamycin (7), is also decreased, leading to a slower elimination.

ACKNOWLEDGMENTS

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LITERATURE CITED