ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1976, p. 173-175

Vol. 10, No. 1
Printed in U.S.A.

NOTES

Triple Crossover Study on Absorption and Excretion of Ampicillin, Talampicillin, and Amoxycillin

L. VERBIST

Department of Microbiology, Academisch Ziekenhuis St. Rafaël, University of Leuven, B-3000, Belgium

Received for publication 8 March 1976

Talampicillin and amoxycillin were shown to be absorbed twice as well as ampicillin in a triple crossover experiment.

In recent years a number of ampicillin derivatives have been synthesized that result in higher drug concentrations in serum after oral administration (1-9). A previous triple crossover study showed that equivalent doses of amoxycillin and pivampicillin gave rise to a twofold and threefold increase of drug serum concentrations in serum, respectively, as compared with ampicillin (8).

The present study compares the absorption and excretion of equivalent doses of talampicillin, the phthalidyl ester of ampicillin, and of amoxycillin with a double dose of ampicillin in 10 healthy volunteers in a randomized crossover fashion. Ampicillin (1,000 mg), talampicillin (742 mg), or amoxycillin (500 mg) was administered after an overnight fast, and breakfast was allowed 2 h later. Blood samples were obtained before and at 1, 1.5, 2, 4, and 6 h after drug administration. Urine samples were collected between 0 to 3, 3 to 6, and 6 to 9 h after drug administration. The antibiotic concentrations were determined with an agar well method using *Bacillus subtilis* ATCC 6633 as the test organism. Further details of this method have been described in a previous paper (8).

All samples were stored at −20 C until the series was complete and were assayed in duplicate on the same day. The calculated regression lines of the standards in serum and saline had a correlation coefficient for ampicillin of $r = 0.977$ and $r = 0.999$, respectively, and for amoxycillin of $r = 0.997$ and $r = 0.995$.

The mean drug concentrations in serum are graphically presented in Fig. 1, which indicates that the curves for the three drugs are superimposed, although there is an earlier peak with talampicillin and slightly more persistent levels with ampicillin and amoxycillin.

The average of the individual peak drug concentrations in serum (Table 1) of talampicillin (7.41 μg/ml) and amoxycillin (6.78 μg/ml) were somewhat higher than those obtained after an equivalent double dose of ampicillin (6.20 μg/ml).

The surface of the "area under the curve" was geometrically calculated for each volunteer as previously described (8). Dividing this surface value by the total time in hours resulted in an average drug concentration in serum per hour over a 6-h period. This provided an excellent therapeutic index for comparison since it took into account early as well as late drug concentrations in the serum. These values were found similar for all three drugs, namely, 3.05 μg/ml for ampicillin, 2.62 μg/ml for talampicillin, and 3.06 μg/ml for amoxycillin (Table 1). The mean cumulative quantities of active compounds recovered from urine and expressed as a percentage of the administered dose are shown in Fig. 2. On the average, 41.5% of the ampicillin dose, 65.6% of the talampicillin dose, and 65.7% of the amoxycillin dose were excreted in 9 h. With each antibiotic, at least two-thirds of the excreted dose was recovered during the first 3 h, and more than 98% was recovered within 6 h.

Similar results have been obtained with amoxycillin in a previous study, namely, a mean peak drug concentration in serum of 8.3 μg/ml, an average serum level per hour of 3.1 μg/ml, and a urinary recovery of 64.2% (8). However, the urinary recovery of ampicillin (41.5% of a 1,000-mg dose) in this study was nearly twice as high as in the previous study (21.8% of a 500-mg dose). Since the major difference between both studies was the delay between drug administration and breakfast (30 min in the first study, 2 h in the present study), it may be concluded that food intake had a major adverse influence on the absorption of ampicillin but not on amoxycillin.

The differences in absorption between the three antibiotics can be evaluated on the basis

TABLE 1. *Drug concentrations in serum and recovery in urine*

Drug	Peak concn in serum (μg/ml)			Avg concn in serum/h (μg/ml)			Recovery (%) in urine (0 to 9 h)		
	Mean	SD[a]	V	Mean	SD	V	Mean	SD	V
Ampicillin (1,000 mg)	6.20 (3.3-10.7)[b]	2.57	0.41	3.05 (2.0-5.1)	1.07	0.35	41.5 (23.2-68.1)	15.1	0.36
Talampicillin (742 mg)[c]	7.41 (5.2-10.1)	1.59	0.21	2.62 (1.9-3.6)	0.55	0.21	65.5 (56.5-76.3)	6.4	0.10
Amoxycillin (500 mg)	6.78 (4.2-10.1)	1.94	0.29	3.06 (2.2-4.4)	0.67	0.22	65.7 (40.9-93.9)	14.5	0.22

[a] SD, Standard deviation; V = standard deviation/mean, dispersion coefficient.
[b] Extreme values are given in parentheses.
[c] Equivalent to 500 mg of ampicillin.

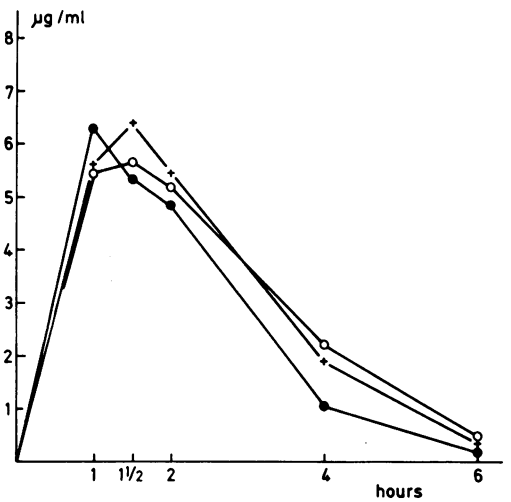

FIG. 1. *Mean drug concentrations in serum after oral administration of: (○) ampicillin, 1,000 mg; (+) amoxycillin, 500 mg; (●) talampicillin, 742 mg (equivalent to 500 mg of ampicillin).*

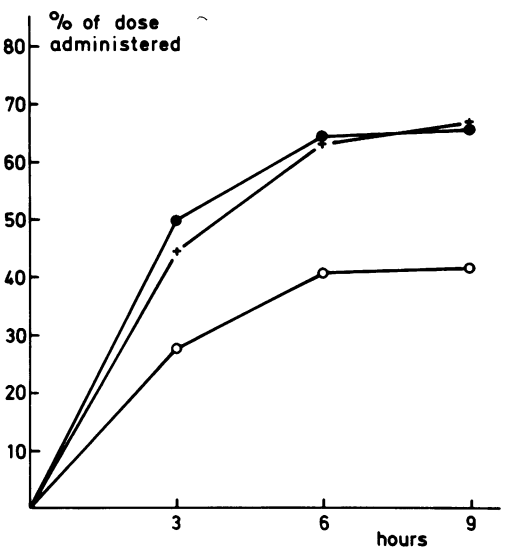

FIG. 2. *Cumulative renal excretion of active compounds after oral administration of: (○) ampicillin, 1,000 mg; (+) amoxycillin, 500 mg; (●) talampicillin, 742 mg (equivalent to 500 mg of ampicillin).*

of three main criteria: the average of the individual peak serum levels, the average serum level per hour over a 6-h period, and the percentage of recovery of active compounds in urine within 9 h (Table 1). From these data it is obvious that talampicillin and amoxycillin are absorbed twice as well as ampicillin since half the equivalent dose provides approximately the same antimicrobial activity in serum.

The degree of uniformity of individual data within the same group of subjects is best expressed by the dispersion coefficient, calculated by the formula V = standard deviation/mean: the smaller this dispersion coefficient, the less variability within the values of the individuals. As measured on the dispersion coefficient of all three criteria, the uniformity was highest with talampicillin and lowest with ampicillin. This greater uniformity in absorption of amoxycillin, and especially of talampicillin, over ampicillin is a further advantage of these antibiotics with regard to the reliability of an oral chemotherapy.

This investigation has been supported by a grant from Continental Pharma.
The technical assistance of Claire Van Ourti is gratefully acknowledged.

LITERATURE CITED

1. **Bodey, G. P., and J. Nance.** 1972. Amoxycillin: in vitro and pharmacological studies. Antimicrob. Agents Chemother. 1:358-362.
2. **Clayton, J. P., M. Cole, S. W. Elson, and H. Ferres.** 1974. BRL.8988 (talampicillin), a well-absorbed oral form of ampicillin. Antimicrob. Agents Chemother. 5:670-671.
3. **Croydon, E. A. P., and R. Sutherland.** 1971. α-Amino-p-hydroxybenzylpenicillin (BRL 2333), a new semisynthetic penicillin: absorption and excretion in man, p. 427-430. Antimicrob. Agents Chemother. 1970.
4. **Foltz, E. L., J. W. West, I. H. Breslow, and H. Wallick.** 1971. Clinical pharmacology of pivampicillin, p.

442–454. Antimicrob. Agents Chemother. 1970.
5. **Jordan, M. C., J. B. de Maine, and W. M. M. Kirby.** 1971. Clinical pharmacology of pivampicillin as compared with ampicillin, p. 438–444. Antimicrob. Agents Chemother. 1970.
6. **Neu, H. C., and E. B. Winshell.** 1971. Pharmacological studies of 6[D(−)α-amino-p-hydroxyphenylacetamido]penicillanic acid in humans, p. 423–426. Antimicrob. Agents Chemother. 1970.
7. **Sutherland, R., and G. N. Robinson.** 1971. α-Amino-p-hydroxybenzylpenicillin (BRL 2333), a new semisynthetic penicillin: in vitro evaluation, p. 411–415. Antimicrob. Agents Chemother. 1970.
8. **Verbist, L.** 1974. Triple crossover study on absorption and excretion of ampicillin, pivampicillin, and amoxycillin. Antimicrob. Agents Chemother. 6:588–593.
9. **von Daehne, W., W. O. Godtfredsen, K. Roholt, and L. Tybring.** 1971. Pivampicillin, a new orally active ampicillin ester, p. 431–437. Antimicrob. Agents Chemother. 1970.