

Pharmacokinetic Comparison of Oral Bacampicillin and Parenteral Ampicillin

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Bacampicillin is a new oral prodrug which is rapidly converted to ampicillin during absorption from the gastrointestinal tract. High serum peaks of ampicillin are obtained. Bacampicillin orally was compared pharmacokinetically with parenteral ampicillin (intravenously and intramuscularly). A cross-over study on healthy volunteers showed that ampicillin concentrations after equimolar doses of bacampicillin orally and ampicillin intramuscularly were of the same order. The mean of the individual peak values (regardless of time of occurrence) after a dose of 800 mg of bacampicillin was $13.1 \pm 3.8 \mu\text{g/ml}$. Absorption rates of the two doses were similar, as were their distribution volumes (approximately 25% of the body weight). Bioavailability was 87% for bacampicillin, compared to 71% for ampicillin.

Bacampicillin (code number A 2393) is a new semisynthetic ester of ampicillin, chemically 1'-[(ethoxycarbonyl)oxy]ethyl-6-(D- α -aminophenylacetamido) penicillinate-hydrochloride, with a pK_a of 6.8 at 25°C. The substitution at the ampicillin thiazolidine carboxy group makes bacampicillin less polar (higher lipid solubility at physiological pH) without appreciably changing the water solubility; therefore it has a better bioavailability than ampicillin upon oral intake (2, 20, 26a).

Upon absorption, bacampicillin is rapidly hydrolyzed to ampicillin (2; A. Swahn, Ph.D. thesis, Karolinska Institute, Stockholm, Sweden, 1974), which is the antibacterial principle.

In this report, the pharmacokinetic characteristics of oral bacampicillin will be compared with those of ampicillin injected intravenously and intramuscularly.

MATERIALS AND METHODS

Plan of study. After fasting at least from midnight, the subjects received either 800 mg of bacampicillin (batch F81) orally (2 tablets) or equimolar doses of 556 mg of ampicillin intramuscularly (i.m.) (batch ZF 437FB), or 556 mg of ampicillin intravenously (i.v.) (batch ZF 437FA). The drugs were provided by Astra Läkemedel AB, Södertälje, Sweden. The tablets were taken with 100 ml of water. The parenteral doses were diluted in pyrogen-free, sterile water immediately before use, the i.m. dose in 2 ml and the i.v. dose in 5 ml. The i.m. doses were injected into the buttock, the i.v. as 5-min bolus injections directly into an arm vein. A cross-over design insured that all individuals received all three doses. Food was restricted for after drug administration.

Subjects. Ten healthy male medical student volunteers participated in the study. To ensure their health, they were given a physical examination and studied by urinalysis and blood tests for hemoglobin, electron spin resonance, creatinin, bilirubin, alkaline phosphatase, total serum protein, and albumin contents. All volunteers were informed of the nature of the study, the possible effects on bacterial flora, and the role of ampicillin as an allergen. None had previous allergies or unexplained reactions to penicillins or cephalosporins. The volunteers were covered by insurance in connection with the study. All other pharmaceuticals were banned during the period of study.

The average age of the subjects was 22.5 ± 2.1 years, weight was 70.6 ± 4.7 kg, and height was 181.0 ± 5.9 cm.

Sampling. Blood samples were obtained from a short indwelling arm vein catheter (Venflon) at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 h after drug intake. Serum was separated within an hour and stored at -70°C until analysis within 2 weeks. A stock solution of ampicillin for assay standards was frozen together with the samples.

Assays. Antibiotic assays were done with an agar well procedure similar to one used previously (1). *Staphylococcus aureus* ATCC 6538p was used as the test organism. Sodium ampicillin of certified potency for use as a standard was received from Astra Läkemedel AB, Södertälje, Sweden.

Pharmacokinetic calculations. Pharmacokinetic characteristics were based on an iterative nonlinear curve-fitting procedure for each dose using the program BMD07R (5) for oral and i.m. data and program FARM (Norsk Regnesentral, Oslo) for i.v. data.

Serum concentrations after extravascular doses were adjusted to a first-order, one-compartment open model with first-order absorption and the i.v. data to a first-order two-compartment open model. Derived

parameters were obtained as previously defined (10, 24, 25, 28).

Statistical evaluation. The distribution being non-normal for some of the variables, the Wilcoxon signed rank test was used for the analysis of significance of differences (29).

RESULTS

Serum concentrations. The mean ampicillin serum concentrations are shown in Table 1. Oral bacampicillin rendered approximately the same ampicillin serum levels as ampicillin i.m. Therapeutic concentrations were reached after 10 to 20 min. The mean maximum concentration after one dose, c'_{max} , of each individual was 13.1 ± 3.8 $\mu\text{g/ml}$ after bacampicillin and 11.3 ± 3.5 $\mu\text{g/ml}$ after ampicillin i.m. The values for the two-compartment hybrid intercepts of ampicillin i.v. were $A = 89.4 \pm 43.6$ and $B = 11.4 \pm 3.22$ $\mu\text{g/ml}$.

Absorption rate. The apparent lag time before absorption as estimated by the feathering method (25) is longer for oral bacampicillin (0.21 ± 0.08 h) than for ampicillin i.m. (0.13 ± 0.07 h).

The absorption rate constant (k_1) after oral bacampicillin and ampicillin i.m. are listed in Table 2. They were of the same order.

Constants of disposition and transport between compartments. Table 2 shows the rate constants for serum disposition (k_2 , α , β), elimination from the body (k_E), and for transport between the central and the peripheral compartments (k_{12} , k_{21}). The slopes of the mean serum curves for the three types of dosage are similar. The mean serum half-life ($t_{1/2\beta}$) calculated for i.v. doses of ampicillin was insignificantly higher than that after i.m. or oral doses of bacampicillin. The difference between k_{12} and k_{21} was statistically significant ($P < 0.05$).

Distribution. The apparent distribution volumes are shown in Table 3. The value of V_D was 25.5 liters after bacampicillin and 22.2 liters after ampicillin i.m. The $V_{d,\beta}$ was 23.7 liters after the i.v. bolus dose. These three values were of the same order. The apparent volume of distribution for the peripheral compartment was $V_T = 17.5$ liters.

TABLE 1. Serum concentrations of ampicillin after ampicillin and bacampicillin doses^a

Drug	Serum concn ($\mu\text{g/ml}$) at hours after dose:							
	0.25	0.5	0.75	1	1.5	2	4	6
Bacampicillin	2.0 ± 2.06	5.6 ± 3.48	8.8 ± 4.42	11.1 ± 4.55	8.7 ± 1.89	7.0 ± 1.82	1.7 ± 0.62	0.46 ± 0.33
Ampicillin i.v.	41.7 ± 13.4	20.9 ± 8.17	10.5 ± 2.29	8.0 ± 1.52	4.9 ± 1.14	3.4 ± 1.06	1.1 ± 0.69	0.19 ± 0.18
Ampicillin i.m.	3.6 ± 0.98	6.8 ± 1.43	10.3 ± 3.28	10.0 ± 4.00	7.3 ± 2.36	4.6 ± 1.65	1.1 ± 0.57	0.27 ± 0.17

^a Mean of 10 normal volunteers \pm standard deviation. Drug doses: bacampicillin, 800 mg orally; ampicillin, 556 mg i.m. or i.v.

TABLE 2. Rate constants of ampicillin transport and disposition^a

Drug	k_1 (h^{-1})	k_2 (h^{-1})	α (h^{-1})	β (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	$t_{1/2\beta}$ (h)	k_E (h^{-1})
Bacampicillin	1.400 ± 0.508	0.776 ± 0.115					0.91 ± 0.14	
Ampicillin i.m.	1.750 ± 0.630	0.823 ± 0.153					0.88 ± 0.21	
Ampicillin i.v.			4.24 ± 1.27	0.610 ± 0.080	1.72 ± 0.78	1.07 ± 0.27	1.16 ± 0.16	2.45 ± 0.70

^a Dosages: bacampicillin, 800 mg orally; ampicillin, 556 mg i.m. or i.v. Mean \pm standard deviation. Symbols: k_1 , absorption rate constant; k_2 elimination rate constant; α , hybrid serum slope (disposition) constant of distribution phase; β , hybrid serum slope (disposition) constant of elimination phase; k_{12} , rate constant of transport from the central to the peripheral compartment; k_{21} , rate constant of transport from the peripheral to the central compartment; $t_{1/2\beta}$, serum half-life; k_E , overall elimination rate constant.

TABLE 3. Distribution characteristics of ampicillin

Drug	V_D (liter)	Δ_D (liters/kg)	$V_{d,ss}$ (liter)	$V_{d,\beta}$ (liter)
Bacampicillin	25.45 ± 6.21	0.362 ± 0.094		
Ampicillin i.m.	22.2 ± 7.8	0.315 ± 0.111		
Ampicillin i.v.			13.5 ± 5.14	23.7 ± 5.4

^a After 800 mg of bacampicillin orally or 556 mg of ampicillin i.m. or i.v. Symbols: V_D , distribution volume; Δ_D , distribution coefficient ($V_D/\text{body weight}$); $V_{d,ss}$, distribution volume at steady state (24); $V_{d,\beta}$, distribution volume at apparent distribution balance (10). Mean \pm standard deviation.

Total body clearance. The total body clearance has been calculated from the i.v. dose as $Cl_T = V_c \cdot k_E = 255.2$ ml/min. The V_c is the central distribution volume, which was 6.25 ± 2.02 liters.

Bioavailability. The bioavailability of the two extravascular dosage forms was assessed on the basis of the Dost theorem of equivalence of corresponding areas under curves of serum concentration versus time (F) following equal doses of the same drug (7). The i.v. dose is used as the 100% reference point.

The area under the serum curve till infinity after the i.v. dose was 40.3 ± 7.19 $\mu\text{g}/\text{h}$ per ml. Bacampicillin had a mean bioavailability of $87 \pm 21.8\%$ and ampicillin i.m. was $71.0 \pm 21.4\%$. The ratio of the areas under the curves, $F_{\text{bacampicillin}}$ to $F_{\text{ampicillin i.m.}}$, was 1.2.

DISCUSSION

Bacampicillin is a prodrug which is rapidly and completely hydrolyzed to render plain ampicillin during or immediately after absorption. Even with the most sensitive technique, bacampicillin has never been found in serum of humans or animals (2; A. Swahn, Ph.D. thesis). Thus, nonspecific artifacts derivable from degradation in vitro following blood sampling are not applicable to bacampicillin as with, e.g., hecaticillin (14). The blood samples do not contain largely inactive bacampicillin which liberates ampicillin only after sampling. Thus, both pharmacokinetic evaluations and bioavailability estimates are validly based on ampicillin.

The serum concentrations observed after bacampicillin and ampicillin i.m. or i.v. were of the same order as implemented by similar doses in other investigations (3, 5, 11, 13-15, 18, 20-22, 26-27). It is important to note that the mean values obtained here are completely superimposable on the curves of Simon (26) after the same doses of bacampicillin orally and ampicillin i.v. After 1 h, the serum levels after oral bacampicillin were above those obtained by both equimolar parenteral doses of ampicillin. After 6 h, serum concentrations after bacampicillin were twice those observed after the other doses. The serum concentrations after bacampicillin were two to four times higher than after comparable doses of ampicillin orally, when only 2-4 $\mu\text{g}/\text{ml}$ would be expected (12, 16, 17, 21, 26, 26a).

A concentration of 5 μg of ampicillin per ml is often considered an upper level of susceptibility, since 70 to 80% of *Escherichia coli* require for inhibition minimum inhibitory concentrations below this level (9, 23). Except for rare beta-lactamase-producing strains, *Haemophilus influenzae* requires minimum inhibitory concen-

trations of ampicillin below 1.0 $\mu\text{g}/\text{ml}$ (30). The i.m. doses used in these experiments would render serum levels of ampicillin above 5 $\mu\text{g}/\text{ml}$ for about 2 h, of bacampicillin for some 3 h.

The presently calculated pharmacokinetic parameters were of the same order as found by others (3-5), although differing values have also been reported for similar doses (19). Bolme et al. (3), with 0.5 g of ampicillin i.v., found $\alpha = 4.5$ and $\beta = 0.79$ h^{-1} , compared to $\alpha = 4.2$ and $\beta = 0.61$ h^{-1} in this study. The k_{12} and k_{21} were 1.60 and 1.77 h^{-1} in the former study (3), compared to the present 1.34 and 1.07 h^{-1} . The $V_{d,\beta}$ of 23.7 liters was slightly lower than the 27 liters observed by Dittert et al. (4), but higher than the 17.9 liters observed by Jusko and Lewis (14). The bioavailability of bacampicillin (87%) and that of ampicillin i.m. (71%) are both above the 40 to 55% noted for ampicillin tablets or capsules (3). Similar i.m. bioavailability has been found by others (8, 23), although up to 90% has been found (25).

It would appear that bacampicillin is favorable in terms of absorption rate and percentage absorbed. The ampicillin levels rendered by bacampicillin are above those after equimolar sodium ampicillin i.m. or i.v. for substantial portions of a normal dosage interval.

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