STUDIES ON THE BIOAVAILABILITY OF SOME BACAMPICILLIN SALTS

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(Received for publication October 22, 1984)

Among the new ampicillin esters, synthesized to obtain a higher bioavailability, the most interesting one is the 1-ethoxycarbonyloxyethyl ester, bacampicillin[1]. It is used as the hydrochloride which has a bitter taste requiring masking in paediatric formulations.

In this paper we report the synthesis and the rat bioavailability of two sparingly soluble and tasteless salts of bacampicillin with *o*-methoxyphenoxyacetic acid (**1a**) and naphtalene-2-sulfonic acid (**2a**) and one readily soluble salt with phosphoric acid (**3a**).

Bacampicillin hydrochloride[2] was converted into the free base by treatment of its aqueous solution with 1 equivalent of $NaHCO_3$ and extraction with ethyl acetate. The solvent was evaporated, the residual oil dissolved in methylene chloride or ethyl acetate and treated with 1 equivalent of *o*-methoxyphenoxyacetic acid, naphtalene-2-sulfonic acid or phosphoric acid respectively. Concentration at reduced pressure gave the salts that were subsequently purified through crystallization. The bioavailabilities in rats of the three salts were compared to those of ampicillin trihydrate and bacampicillin hydrochloride by measuring the plasma levels after oral administration of the compounds in doses equivalent to 100 mg (286.3 μmol)/kg of anhydrous ampicillin.

Wistar rats, average weight 290 g, 16 animals per compounds and fasting for 12 hours before the experiment, were used. Four rats were sacrificed respectively 20, 40, 60 and 120 minutes after the oral administration of each of the five compounds in 5% arabic gum (20 ml/kg). Plasma levels were assayed for ampicillin by an agar diffusion method using *Micrococcus luteus* ATCC 9341 as the assay organism[3].

The plasma levels of ampicillin obtained after administration of **1a** and **2a** were lower than those of bacampicillin hydrochloride and **3a** and similar to those of ampicillin (Table 1). It seems that the elimination of the bitter taste in bacampicillin by making it less soluble in water causes a reduction of its bioavailability.

Experimental

Ampicillin 1-ethoxycarbonyloxyethyl ester hydrochloride (10 g) was dissolved in water (80 ml) at 5°C. 1.7 g of $NaHCO_3$ was added and the mixture was extracted twice with ethyl acetate (100+50 ml). The combined extracts were washed with saturated sodium chloride solution, dried and evaporated to give a residual oil which was dissolved in 20 ml of methylene chloride.

3.24 g of *o*-methoxyphenoxyacetic acid were added and the clear solution was evaporated to a small volume to give a precipitate which was recrystallized from ethanol - ether yielding 8.7 g of the white salt. MP 83~86°C (dec); $[\alpha]_D^{20}$ +100.8° (*c* 2, EtOH). Bacampicillin and *o*-methoxyphenoxyacetic acid, determined by reversed-phase liquid chromatography (Lichrosorb RP 8~10 Å) using 60% acetonitrile in phosphate buffer (pH 8.0) as the mobile phase (detection

Table 1. Plasma levels of ampicillin in rats after oral administration of **1a**, **2a**, bacampicillin hydrochloride, **3a** and ampicillin trihydrate (286.3 μmol/kg).

Compounds	Plasma levels of ampicillin† (μg/ml) (means±s.e.m.)				AUC* (μg/ml·minute)
	20 minutes	40 minutes	60 minutes	120 minutes	
1a	3.61±0.38	4.09±0.62	2.83±0.38	1.65±0.45	319.8
2a	3.61±0.45	4.15±0.65	2.79±0.39	1.77±0.54	317.1
Bacampicillin·HCl	9.74±0.88	9.39±3.90	4.25±1.16	1.43±0.18	595.7
3a	8.68±1.36	11.21±2.31	5.19±0.42	1.40±0.55	647.4
Ampicillin·$3H_2O$	3.60±0.45	4.04±0.65	2.79±0.37	1.71±0.53	315.7

† 4 animals/time.

* Area under curve calculated according to the trapezoidal rule.

UV 213 nm) were 71.62% and 28.03% respectively. The aqueous solubility was less than 0.01% at 25°C.

To a solution of ampicillin 1-ethoxycarbonyloxyethyl ester in methylene chloride, prepared as described above, 4.16 g of naphtalene-2-sulfonic acid were added. Removal of the solvent gave a crystalline residue which was recrystallized from 2-propanol - ether to give 7.35 g of the salt. MP 115~117°C (dec); $[\alpha]_D^{20}$ +45.1° (*c* 2, EtOH).

Bacampicillin and naphtalene-2-sulfonic acid, determined as above, were 69.14% and 30.77% respectively. The aqueous solubility was less than 0.01% at 25°C.

To a solution of ampicillin 1-ethoxycarbonyloxyethyl ester (from 10 g of the hydrochloride) in ethyl acetate, 0.978 ml of 85% phosphoric acid were added. The solution was concentrated to a small volume and the precipitate (7.9 g) filtered. Recrystallization from methanol - ether afforded 6.25 g of the salt. MP 112~114°C (dec); $[\alpha]_D^{20}$ +94.05° (*c* 2, EtOH). Bacampicillin, determined as above, was 82.6%. The aqueous solubility was greater than 10% at 25°C.

References

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