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BRL.8988 (Talampicillin[1]), a Well-Absorbed Oral Form of Ampicillin

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The phthalidyl ester (BRL.8988, talampicillin) of ampicillin gave serum levels in man two and a half times those obtained with ampicillin itself.

Ampicillin, D-α-aminobenzylpenicillin (Ia, Fig. 1) is a widely used semisynthetic penicillin. When orally administered to man, from 30 to 50% of the drug is excreted unchanged in the urine (5). In an attempt to improve absorption, esters of ampicillin have been made which, being more lipid soluble than the parent acid, might be expected to show improved absorption from the gut (1). Penicillin thiazolidine esters, however, are devoid of useful antibacterial activity, and therefore a necessary requirement for an ester used to facilitate absorption must be its ready hydrolysis in the body to the parent penicillin-free acid. Simple alkyl and aryl esters do not meet this requirement.

The pivaloyloxymethyl ester of ampicillin, pivampicillin (Ib), is an example of a class of acyloxymethyl esters, first described by Jansen and Russell (4), which is well absorbed and undergoes hydrolysis in the body to give peak levels of ampicillin greater than twice those obtained with ampicillin itself (3). We now wish to describe a further class of novel, hydrolyzable ampicillin esters in which the ester group is incorporated in a lactone function (British Patent Application Numbers 19604/71, 294431/72, and 5345/74 [*Beecham Research Laboratories*]).

Phthalidyl D-α-aminobenzylpenicillanate (Ic, BRL.8988, talampicillin) may be prepared by the condensation of ampicillin, protected as its enamine, with bromophthalide. The enamine-protecting group was removed by mild acid treatment to give BRL.8988 as its hydrochloride, obtained as a 1:1 mixture of isomers epimeric at the chiral center in the ester moiety. The individual epimers were also prepared and shown to possess similar hydrolysis and absorption properties. The data below refer to the epimeric mixture.

[1] Talampicillin is the British Pharmacopoeia Commission approved name for BRL.8988

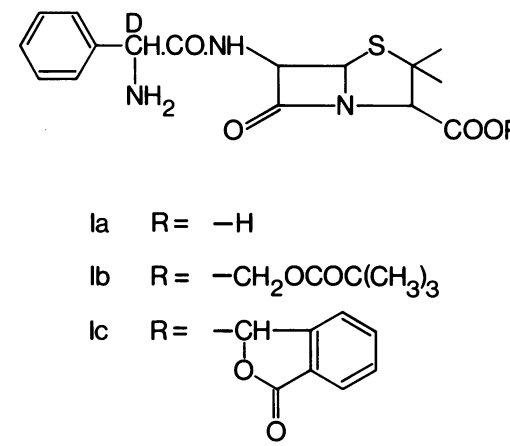

FIG. 1. *Structure of ampicillin (Ia), pivampicillin (Ib), and BRL.8988 (talampicillin) (Ic).*

To determine the susceptibility of BRL.8988 to hydrolysis, rates were measured over a period of 25 min in aqueous solution and human tissue homogenates as outlined in Table 1. Pivampicillin was included for comparison. It will be observed that, in buffer at pH 7.4, both BRL.8988 and pivampicillin hydrolyzed slowly to ampicillin, the rate for BRL.8988 being slightly faster. At pH 2.0 both compounds were stable to hydrolysis. In human small intestine homogenate both compounds were completely hydrolyzed after 15 min to ampicillin and this was also the case in human whole blood. However, in 2% human blood and in human liver homogenate, BRL.8988 was hydrolyzed at an appreciably faster rate than pivampicillin. Likewise in 90% human serum, BRL.8988 was 80% hydrolyzed to ampicillin after 3 min compared with less than 10% hydrolysis of pivampicillin.

A 371-mg amount of BRL.8988 as its hydrochloride, equivalent to 250 mg of ampicillin,

TABLE 1. *Hydrolysis of BRL.8988 (talampicillin) in phosphate buffer and human tissue homogenates in comparison with pivampicillin*[a]

Hydrolysis system	Substrate	% Hydrolysis of BRL.8988 or pivampicillin to ampicillin after:			
		3 min	8 min	15 min	25 min
Phosphate buffer, pH 7.4	BRL.8988	<10	<10	24	37
	Pivampicillin	<10	<10	<10	14
2% Human blood in buffer, pH 7.4	BRL.8988	37	50	63	90
	Pivampicillin	<10	<10	16	22
90% Human serum	BRL.8988	80	83	95	83
	Pivampicillin	<10	18	32	36
10% Human small intestine homogenate in buffer, pH 7.4	BRL.8988	79	82	100	100
	Pivampicillin	80	84	100	94
0.02% Human liver homogenate in buffer, pH 7.4	BRL.8988	<10	21	50	66
	Pivampicillin	<10	<10	14	20

[a] Reaction mixtures consisted of BRL.8988 or pivampicillin in 0.05 M potassium phosphate buffer at pH 7.4 or in blood-liver homogenate, or small intestine homogenate diluted in the same buffer. The human serum was 90%. The final concentrations of BRL.8988 and pivampicillin were equivalent to 5.0 μg of ampicillin sodium per ml. The ampicillin formed during the reaction was estimated after rapid separation from ester by electrophoresis in agar at pH 5.5 and bioassaying by overlayering with agar seeded with *Sarcina lutea* NCTC8340. Ampicillin standards were prepared in buffer or tissue homogenates and put through the same procedure.

was orally administered in unformulated, gelatin capsules to 10 fasting human volunteers. A mean peak serum level of 6.2 μg of ampicillin per ml was obtained 1 h after dosing. This was two and a half times the reported mean peak value of 2.6 μg/ml obtained 2 h after an oral dose of 250 mg of ampicillin (6).

This superior absorption of BRL.8988, compared with ampicillin, was also reflected in a higher recovery of drug in the urine. In the above study with BRL.8988, 83% of the dose was recovered in the urine, 69% as ampicillin and 14% as the corresponding penicilloic acid. In the case of 250 mg of oral ampicillin, 43% of the drug was reported to be excreted unchanged in the urine and 11% was excreted as penicilloic acid (2). Biochromatographic examination of the urine from the BRL.8988 study showed ampicillin to be the only microbiologically active component present. There was no evidence of unhydrolyzed ester.

Further data on BRL.8988, which is at present undergoing clinical trial as a broad-spectrum antibiotic, will be reported in detail elsewhere.

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