Biliary excretion of penicillins in the rat

Excretion of penicillins occurs in the bile of animals and man (see for example Stewart & Harrison, 1961; Ayliffe & Davies, 1965 for ampicillin and Acred, Brown and others, 1961; Henegar, Silverman & others, 1961 for methicillin), and there seems to be differences in the amounts of the various penicillins excreted. I now report variations in the biliary excretion of different penicillins in the rat when a standardized technique was used to measure the amounts of penicillin eliminated into the bile and to relate these to the logarithm of partition coefficients and chromatographic R_M-values of the penicillins.

The penicillins used were obtained from the Research Laboratories, Astra Läkemedel AB, Södertälje, Sweden. Rats of the Sprague-Dawley strain, with bile fistulae, 350 g, and under pentobarbitone anaesthesia with the temperature at 38 ± 1°, had the compounds injected into the femoral vein (dose 15 mg/kg) and bile collected for 4 h after administration. Antibiotic concentrations were determined by the cylinder-plate biological assay method (Grove & Randall, 1955), using pseudomonas of the Ellsworth strain for carboxybenzyl penicillin and *Sarcea lutea* ATCC 9341 for the other penicillins. The dilutions for the standard curve were prepared in pooled rat bile and the bile samples were diluted in the same medium to give a concentration within the range of the standard curve. Free acids of the penicillins were extracted with n-octanol from acetate buffer solutions (0·01M, pH 4·70 ± 0·02) and measured (Fujita, Iwasa & others, 1964). The concentrations of penicillins were measured by a hydroxylamine method (Boxer & Everett, 1949). The pK_a values of the various penicillins (for calculation of partition coefficients) were obtained from the literature (Rapson & Bird, 1963; Hon & Poole, 1969). The chromatographic R_M-values $\left[R_M = \log\left(\frac{1}{R_F} - 1\right)\right]$ were according to Biagi, Barbaro & others (1969).

Variations in the bile concentrations of biologically active penicillins were noted (Table 1). The concentration range for benzylpenicillin, ampicillin, methicillin and carboxybenzyl penicillin was 696–838 μg/g bile during the 0–1 h time interval. The concentration range for the other penicillins was 330–398 μg/g bile over 0–1 h. The bile concentration of penicillin gradually diminished during the 1–4 h. The cumulative excretions of penicillins into the bile are in Table 2. The penicillins showing the highest concentrations were also excreted to the greatest extent since the bile flow was of about the same rate in all experiments. Four h after administration, more than 30% of the doses of methicillin, ampicillin or carboxybenzyl penicillin had been eliminated as biologically active penicillin. Benzylpenicillin was also eliminated in

Table 1. *Concentration of biologically active penicillin in the bile after intravenous administration of various penicillins to rats* (15 mg/kg).

Compound	Concentration in bile (μg/g)* 0–1 h	1–2 h	2–4 h
Dicloxacillin	378 ± 76	14 ± 9	2 ± 1
Cloxacillin	330 ± 31	11 ± 2	1 ± 0
Oxacillin	368 ± 41	30 ± 3	1 ± 0
Azidocillin	357 ± 28	99 ± 71	4 ± 2
Pheneticillin	339 ± 45	18 ± 7	1 ± 0
Phenoxymethylpenicillin	398 ± 20	19 ± 1	9 ± 7
Benzylpenicillin	696 ± 110	37 ± 12	1 ± 0
Carboxybenzylpenicillin	838 ± 70	195 ± 50	21 ± 7
Methicillin	836 ± 84	299 ± 90	68 ± 38
Ampicillin	780 ± 146	352 ± 53	57 ± 19

* Each value represents the mean of 3–7 experiments ± s.e.

Table 2. *Cumulative excretion of biologically active penicillin in the bile after intravenous administration of various penicillins* (15 mg/kg) *to rats.* Results expressed as % of the administered dose are given together with the logarithm of the partition coefficients (log P) and chromatographic *RM*-values of the penicillins.

Compound	Amount excreted (%)* 0–1 h	0–2 h	0–4h	log P	R_M
Dicloxacillin	12·3 ± 2·0	12·7 ± 2·0	12·7 ± 2·0	3·24	1·62
Cloxacillin	10·8 ± 1·8	11·1 ± 1·8	11·2 ± 1·9	2·49	1·34
Oxacillin	17·4 ± 1·7	18·8 ± 2·6	18·9 ± 2·6	2·38	1·05
Azidocillin	10·8 ± 1·5	12·7 ± 1·8	12·9 ± 1·9	2·29	—
Pheneticillin	11·8 ± 1·5	12·3 ± 1·7	12·3 ± 1·7	2·20	1·03
Phenoxymethylpenicillin	14·1 ± 0·3	14·7 ± 1·8	15·1 ± 1·8	2·03	0·89
Benzylpenicillin	23·1 ± 3·2	24·0 ± 3·4	24·1 ± 3·4	1·72	0·55
Carboxybenzylpenicillin	27·3 ± 1·7	32·5 ± 2·5	33·2 ± 2·6	1·13	0·46
Methicillin	28·4 ± 4·0	36·3 ± 4·7	38·4 ± 5·1	1·06	0·47
Ampicillin	22·5 ± 5·5	30·6 ± 5·0	33·2 ± 4·8	—	0·07

* Each value represents the mean of 3–7 experiments ± s.e.

appreciable amounts since about 25% of the dose was in the bile. The other penicillins showed a more moderate excretion with a range from 11–19%. Table 2 also shows the logarithm of the partition coefficients and R_M-values of the compounds. When relating the amount of biologically active penicillin excreted in the bile during the 0–4 h period to the logarithm of the partition coefficients or R_M-values of the penicillins, correlation coefficients of −0·87 or −0·84 were found, respectively. This indicates that, with the penicillins used, a relation exists between increasing polarity in the side-chain of the penicillin molecule and biliary excretion. The variation in polarity may express differences in for example inactivation, affinity for transport systems or protein binding of the penicillins.

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