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EXCRETION OF ANTIBIOTICS IN BILE

BY

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The excretion of antibiotics in the bile of rats has been studied. Penicillins, including derivatives of 6-aminopenicillanic acid, are rapidly excreted, reabsorbed and re-excreted, in high concentration, whereas streptomycin, neomycin, paramomycin and chloramphenicol reach lower levels in the bile than in the plasma. p-Aminobenzylpenicillin and D(−)-6-(α-amino-α-phenylacetamido)penicillanic acid, both of which are bactericidal to Salmonellae and other coliforms, produce higher concentrations in the bile than benzylpenicillin (penicillin G). This may be of therapeutic importance.

In the preceding paper (Stewart & Harrison, 1961) we drew attention to the high concentration in which D(−)-6-(α-amino-α-phenylacetamido)penicillanic acid was excreted in the bile, and re-excreted after reabsorption. The penicillin family of drugs differs in this respect from the major antibiotics. Since this difference may be of importance in the therapy of infections of the biliary tract and intestine, we report here the results obtained with a range of antibiotics usually considered eligible for the therapy of such infections.

METHODS

The techniques employed in this study are described in the preceding paper (Stewart & Harrison, 1961). All drugs were used in doses of 100 mg/kg. The following drugs were given intramuscularly only: benzylpenicillin (penicillin G), p-aminobenzylpenicillin, methicillin, streptomycin, paromomycin and neomycin. The following drugs were given intramuscularly and orally: D(−)-6-(α-amino-α-phenylacetamido)penicillanic acid plus L(+)-6-(α-amino-α-phenylacetamido)penicillanic acid, and chloramphenicol.

RESULTS

The concentrations of the different antibiotics in the bile after single doses of 100 mg/kg are shown in Table 1. The penicillins were all present in high concentration within 30 min of an intramuscular injection. Excretion proceeded at a high level for a further hour and then diminished. The highest rate of biliary excretion was that of p-aminobenzylpenicillin (over 20% of the dose in 2.5 hr), then D(−)-6-(α-amino-α-phenylacetamido)penicillanic acid and its L(+) isomer, benzylpenicillin and methicillin, in that order. The peak concentrations in the bile were 15 to 90 times higher than the corresponding blood levels.

The other antibiotics tested (Table 1) were present only in minute amounts in the bile. Streptomycin gave the highest yield in this group, but the total excretion

TABLE 1

CONCENTRATIONS (μG/ML.) (AND STANDARD ERRORS) OF ANTIBIOTICS IN THE BILE OF RATS DOSED WITH 100 MG/KG INTRAMUSCULARLY

(−)-6-(α-Amino-α-phenylacetamido)penicillanic acid=BRL 1341, the L(+) isomer=BRL 1060

Hr after injection	Penicillins								Chloramphenicol
	Benzyl	p-Aminobenzyl	BRL 1060	BRL 1341	Methicillin	Streptomycin	Neomycin	Paromomycin	
0·5	695±148	2,729±115	340±77	1,385±161	377±57	6·0	3·0	4·0	1·2
1·5	297±146	2,035±129	446±61	1,344±224	399±60	10	2·7	5·0	7·0
2·5	24	414±179	312±58	984±282	145±105	4·0	1·7	3·0	1·0
3·5			88		35			4·0	
4·5			49		14			Trace	
5·5			26						
5·5–20	43	43	23	30		0	0·6	0	0
Plasma (1 hr)	50	40	35	16	29	66		80	20

(0.08% of the dose) and the peak concentrations (10 μg/ml. or less) were very low indeed compared with any of the penicillins (Fig. 1). Peak values, occurring at 0.5 to 1.5 hr after injection, were much lower than the corresponding plasma levels. Streptomycin and paromomycin were not detectable after this period, but a trace of neomycin was present in the samples of bile collected overnight. When given intramuscularly, chloramphenicol was not detectable after 2.5 hr, but, when given orally, this drug was excreted more slowly in the bile, producing a higher concentration (2.5 μg/ml.) in the overnight sample than in earlier samples.

The concentrations produced in the bile by the various penicillins were, without exception, vastly higher than the concentrations required for the inhibition of sensitive organisms, whereas the concentrations produced by the other antibiotics were, in this respect, marginal and transient. p-Aminobenzylpenicillin gave the highest concentrations; and this compound, together with D(−)-6-(α-amino-α-phenylacetamido)penicillanic acid, yielded concentrations which were significantly higher than the three other penicillins.

Having been once excreted in the bile, the penicillins were reabsorbed and re-excreted into the duodenum. In the case of p-aminobenzylpenicillin, D(−)-6-(α-amino-α-phenylacetamido)penicillanic acid and its L(+) isomer, re-excretion produced in the bile concentrations which, though much lower than those detected in the primary excretion, were still sufficiently high (10 μg/ml. or more) to be bactericidal toward a wide range of pathogens, including the Salmonellae. In the case of the two acids, bactericidal levels were detected in the bile after oral as well as intramuscular administration, though the peak values (400 μg/ml.) were lower, and were not attained until about 3 hr after dosing. Reabsorption and re-excretion continued so that bactericidal levels (6 to 30 μg/ml.) were still detectable in the bile between 3 and 15 hr. Benzylpenicillin, p-aminobenzylpenicillin and methicillin, being acid-labile, were not tested in this way.

DISCUSSION

It is clear from the results that the various penicillins are rapidly and directly transferred from the blood stream into the bile in high concentration in the rat,

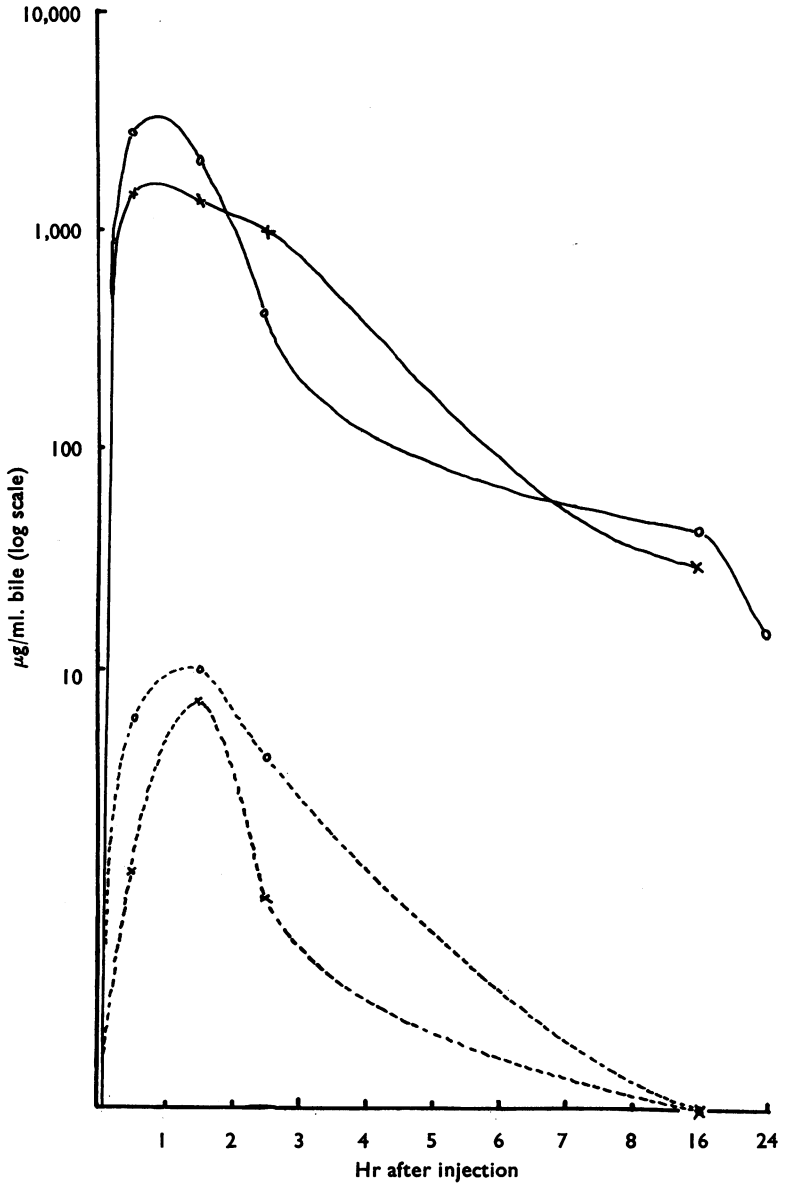

Fig. 1. Biliary excretion (μg/ml.) of 2 penicillins, streptomycin and chloramphenicol in rats given 100 mg/kg intramuscularly. O——O *p*-Aminobenzylpenicillin. X——X D(−)-6-(α-Amino-α-phenylacetamido)penicillanic acid. O - - - O Streptomycin. X - - - X Chloramphenicol.

and that reabsorption and re-excretion of this moiety maintain a bactericidal level of drug in the plasma, bile and upper part of the gut for some hours after a single dose. In contrast, streptomycin, paromomycin, neomycin and chloramphenicol reach lower levels in the bile than in the plasma ; these levels, at peak, are only on the threshold of bacteriostatic activity even when the drugs are given intramuscularly ;

when given orally, as in conventional therapy of an alimentary infection, chloramphenicol, which is well absorbed, may just attain a bacteriostatic concentration in the bile; streptomycin, paromomycin and neomycin, being poorly absorbed, can be discounted in this respect.

It is well known that carriers of certain Salmonellae, especially *S. typhi* and *S. paratyphi B*, may harbour the organisms largely or entirely in the biliary tract, and it is tempting to speculate that the traditional difficulties of eradicating such infection might be due to lack of concentration of eligible antibiotics in the bile, the failure of chloramphenicol in this respect being especially noteworthy. If this explanation is valid, two of the penicillins described here, D(−)-6-(α-amino-α-phenylacetamido)penicillanic acid and its L(+) isomer, might be more promising in biliary carriers, since, as well as being excreted and re-excreted in vastly higher concentration in the bile, both are more actively bactericidal to Salmonellae than any other eligible antibacterial drugs. If infection is localized in the lower bowel as well as in the biliary tract, this reasoning will not apply, since reabsorption will prevent an inhibitory quantity of drug reaching the ileum; in this event, it would seem necessary to administer the drug simultaneously in enteric-coated capsules to ensure its liberation at lower levels in the gut.

The results obtained here in rats may or may not be applicable to man; but it is known that penicillin G is excreted in human bile (Goodman & Gillman, 1955; Sollmann, 1957) and that methicillin behaves similarly (Stewart, Harrison & Holt, 1960). It seems reasonable, therefore, to expect that D(−)-6-(α-amino-α-phenylacetamido)penicillanic acid and its L(+) isomer, which are similar pharmacologically, will behave in the same way in man. The rat has no gall-bladder and the drug levels recorded in the bile derive therefore from direct excretion. It is possible that, in man, a higher local level will result from the considerable concentration which normally affects all other components of the bile in the gall-bladder.

The high rate of immediate excretion of these various penicillins in the bile, coupled with their lack of organic toxicity, suggests that the synthetic penicillins as well as penicillin G do not invoke detoxifying mechanisms in the liver and are therefore equally well eliminated and equally acceptable to the body.

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