The biliary excretion of acebutolol in man

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Practolol is excreted in human bile (Kaye & Kumana, 1974) and acebutolol [(±)-1-(2-acetyl-4-n-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane], has a similar chemical structure, pKa and lipid solubility. Its biliary excretion in two male patients A,B (41, 59 years; 76·4, 65·1 kg) with indwelling T-tubes following bile duct exploration was examined with the patients' consent. Serum bilirubin was 1·71, 1·80 mg dl^{-1}; serum aspartate aminotransferase was 62, 63 Babson units; serum akaline phosphatase was 47, 213 I.U. $litre^{-1}$. Clinical examination and electrocardiography had excluded cardiovascular and respiratory disease. Renal disease was excluded on the basis of normal serum creatinine values for both patients.

About 45 min after a light breakfast each subject's T-tube was gently flushed out with warm sterile isotonic saline under aseptic conditions to establish a free flow of bile. Control samples of plasma, bile and urine were taken 1 h after breakfast. Each patient then swallowed 3 × 100 mg capsules acebutolol hydrochloride (Sectral). Venous blood samples were taken for plasma drug analysis at 1, 2, 3, 4, 6 and 8 h after dosing. Bile and urine were collected 2 hourly up to 8 h and from 8 to 24 h after dosing. Samples were analysed for acebutolol content by the method of Cuthbert & Collins (1975) as modified by Kaye, Kumana & others (1976). These methods measure acebutolol plus its *N*-acetyl metabolite (±)-1-(2-acetyl-4-acetamidophenoxy)-2-hydroxy-3-isopropylaminopropane (M&B 16,942). Bile samples were also examined by thin-layer chromatography using glass plates pre-coated with silica gel DF-B (0·5 mm thick) containing ultraviolet indicator (Camag), and with chloroform–methanol–glacial acetic acid (7:3:1 by volume) as solvent. Bile samples were hydrolysed (5N HCl) and re-assayed for acebutolol to determine whether there was evidence for glucuronide or sulphate conjugates of the drug present in bile.

The plasma concentration of acebutolol in the two patients are shown in Table 1. Reduced absorption of the drug may have occurred in A. Urinary recovery of acebutolol for the two patients is shown in Table 1. Over a 24 h period 13·4 and 39·1% of the dose were recovered from the urine of A and B respectively. This last figure is similar to that found in healthy volunteers (Kaye & others, 1976). Recovery of acebutolol in the bile of the two patients is shown in Table 1. By 24 h 2·7 and 8·5% of the dose had appeared in the bile of A and B respectively. After acid hydrolysis of the bile samples from both patients the concentration of acebutolol as measured remained virtually unchanged.

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Table 1. *Drug concentrations in plasma, urine and bile of the two patients after the oral administration of 300 mg of acebutolol HCl to each.*

Plasma concentrations

Sample time		0h	1h	2h	3h	4h	6h	8h
Plasma concn ($\mu g\ ml^{-1}$)	A	0·00	0·10	0·15	0·31	0·27	0·25	0·23
	B	0·00	0·46	1·60	1·20	1·31	0·89	0·78

Urine concentrations

Sample time (h)	Urine vol. (ml)		Concn ($\mu g\ ml^{-1}$)		Amount in urine (mg)	
	A	B	A	B	A	B
Pretrial	—	—	0·0	0·0	0·0	0·0
0–2	745	50	0·0	97·5	0·0	4·9
2–4	445	35	7·5	830·0	3·3	29·1
4–6	225	245	40·0	105·0	9·0	25·7
6–8	80	180	87·0	100·0	7·0	18·0
8–24	556	755	37·5	52·5	20·9	39·6
Total drug excreted in urine over 24 h (mg)					40·2	117·3
Amount of dose in urine in 24 h (%)					13·4	39·1

Biliary concentrations

Sample time (h)	Bile vol. (ml)		Concn ($\mu g\ ml^{-1}$)		Amount in bile (mg)	
	A	B	A	B	A	B
Pretrial	—	—	0·0	0·0	0·0	0·0
0–2	105	70	8·0	11·0	0·8	0·8
2–4	56	80	31·0	97·0	1·7	7·8
4–6	30	66	33·0	91·0	1·0	6·0
6–8	43	84	29·0	55·5	1·2	4·7
8–24	165	565	20·0	11·0	3·3	6·2
Total drug excreted in bile over 24 h (mg)					8·0	25·5
Amount of dose in bile in 24 h (%)					2·7	8·5

Thin-layer chromatography of bile extracts indicated that the bile samples contained unchanged acebutolol (R_F 0·63) and its *N*-acetyl metabolite (M&B 16,942), (R_F 0·52), in roughly equal amounts, which is qualitatively the same pattern as found in urine. The latter compound could have been formed metabolically from acebutolol by removal of the butyryl group by *N*-deacylation, followed by *N*-acetylation. After acid hydrolysis only the *N*-deacylated derivative (M&B 17,127), (R_F 0·43), was detected in the bile by this method.

The results of this study show that acebutolol, like practolol, is present in human bile following drug administration, and probably does not form glucuronide or sulphate conjugates in the liver to any marked extent. Also, the ratio of peak biliary to peak plasma concentration of drug was 100:1 in A and 60:1 in B. This compares with a ratio of 4:1 with practolol, and suggests that active secretion of acebutolol into bile may produce significant enterohepatic circulation in man.

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The break-up time of artificial pre-ocular films on the rabbit cornea

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The usual treatment for dry-eye diseases is frequent application of artificial 'tears' (Jones & Coop, 1965; Wright, 1971; Lemp, 1973). These normally consist of buffered isotonic solutions of hydrophilic polymers which bear scant resemblance to the natural pre-ocular film. Lemp, Dohlman & others (1971) have found that the break-up time (BUT) of the natural film in the absence of blinking is shorter in some human dry-eye diseases than in normals and the increase in this interval has been used as a criterion of the efficacy of artificial tears (Lemp, Goldberg and Roddy, 1975). The rabbit corneal surface resembles that of the human in a number of respects (Ehlers, 1970) and although differing in others it is likely that solutions forming stable pre-ocular films in the rabbit would have properties of value in the formulation of artificial tears for man. Blinking and pathological corneal changes might affect the performance of a given solution in the clinic, but for comparison of different solutions the rabbit is probably an adequate model. This report, then, describes the BUT of films formed on the corneas of anaesthetized rabbits with solutions of hydrophilic polymers and with commercial artificial tears.

Experiments were conducted in a darkened air-conditioned room. Male rabbits (3·5–5·5 kg) were anaesthetised with chlorpromazine (May and Baker) 25 mg kg^{-1} intramuscularly plus pentobarbitone sodium (Nembutal Veterinary, Abbot) 25–30 mg kg^{-1} intravenously. Each animal was wrapped in a homeothermic blanket (Electrophysiological Instruments) and placed prone in an aluminium holder in front of a slit-lamp biomicroscope. One eye was held open with a speculum. The image of a white grid against a black background was projected on to the cornea using a mirror galvanometer projector (Type 4754, Tinsley) and its reflection was viewed with the biomicroscope. As long as the pre-ocular film was intact the image was clearly seen, but as the film disintegrated the image broke up. It was found that the BUT was highly reproducible. The solution for test was applied liberally to the cornea and the film breakup awaited, whereupon 50 μl was carefully applied over the cornea with a micropipette and the BUT of the resultant film observed. Each solution was tested on one eye of three or four rabbits. The polymers investigated were hydroxyethylcellulose (Natrosol 250 M, Hercules Powder Co.), hydroxypropylmethylcellulose (Methofas PM 4500, ICI), polyvinylalcohols (Gohsenol N300, GL05 and GH17, Nippon Gohsei), polyethyleneoxide (Polyox WSR-301, Union Carbide) and methylcellulose (Celacol M450GP, British Celanese), each dissolved in distilled water.

In concentrations where the polymer solutions were mobile liquids there was, in all cases, a good approximation to a straight line relation between BUT and concentration. In addition, a measurement of viscosity of the polymer solutions was made with a Brookfield viscometer. Solutions were maintained at 25° and the determinations performed with spindle 2 at 30 rev min^{-1}. The results indicate that BUT increased more for a given increase in viscosity with solutions containing low concentrations of polymer than with solutions containing high concentrations. Since some of the solutions would be non-Newtonian, interpretation of these results is difficult. However, in Table 1 are mean BUT values corresponding to several viscosities for each polymer,

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Table 1. *Pre-ocular film mean break-up time related to solution viscosity for several polymers. Results of experiments on one eye of each of four rabbits.*

Viscosity mPa s	Pre-ocular film mean break-up time(s) ± s.e.m.						
	Hydroxyethyl-cellulose	Hydroxypropyl-methylcellulose	Polyethylene-oxide	Polyvinyl alcohol GH-17	Polyvinyl-alcohol N-300	Polyvinyl-alcohol GL-05	Methyl-cellulose
10	33·3 ± 0·7	31·0 ± 3·3	48·8 ± 4·5	36·3 ± 0·9	57·5 ± 6·3	50·4 ± 2·4	38·8 ± 1·3
15	63·3 ± 2·4	51·5 ± 5·7	66·0 ± 5·5	54·0 ± 4·2	73·2 ± 8·3	73·9 ± 5·3	62·0 ± 5·2
25	92·0 ± 1·2	73·7 ± 6·5	88·3 ± 5·7	83·0 ± 8·6	96·7 ± 13·2	108·0 ± 7·1	111·5 ± 7·1
50	121·0 ± 5·9	107·7 ± 6·9	130·8 ± 8·9	131·8 ± 10·4	134·3 ± 27·3	—	132·0 ± 14·6
75	139·3 ± 8·5	130·0 ± 7·5	157·3 ± 11·9	168·8 ± 7·1	151·5 ± 38·3	—	140·0 ± 13·9
100	153·0 ± 9·8	147·8 ± 7·8	161·7 ± 12·4	194·8 ± 4·1	—	—	145·3 ± 13·4
150	173·5 ± 9·8	176·0 ± 8·9	190·3 ± 12·1	235·3 ± 5·3	—	—	—
200	190·3 ± 9·5	193·5 ± 10·6	218·7 ± 13·3	257·0 ± 10·2	—	—	—