Comparative uptake of quinine and quinidine in rat lung

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Many basic amine drugs have been shown to be accumulated in lung tissue by a combination of a saturable binding and non-saturable partitioning process (Anderson et al 1977). The binding component is comprised of relatively non-specific sites common to a diverse range of basic amine drugs (Anderson et al 1973; Minchin et al 1979; Lau & Henderson 1978). While the specificity of these pulmonary sites is generally low, the distribution of mepivacaine (Aberg 1972) and methadone (Chi & Dixit 1977) has been shown to be stereoselective favouring the dextrorotatory isomer. Quinine (Qn) and its diastereoisomer quinidine (Qd) are preferentially taken up in lung tissue in vivo (Hiatt & Quinn 1945; Iven 1977) and in both anaesthetized and conscious dogs, Hiatt & Quinn found that quinine levels in lung were greater than those of quinidine after similar intravenous doses of the two drugs. In the present study, the stereospecificity of uptake of Qn and Qd in rats has been investigated in isolated perfused lung preparations and after intravenous administration in conscious animals.

Male Wistar rats (200–220g) were used. A single pass perfused lung preparation was used (Eling et al 1975) with a perfusion medium consisting of Krebs-Henseleit isotonic bicarbonate buffer containing 4·5% bovine serum albumin and 5 mM glucose. Qn or Qd (1,5,10 or

15 μg HCl salt ml^{-1}) was added to the medium and the lungs perfused at a rate of 6·4 ml min^{-1} for 10 min during which time sequential samples of the effluent were collected. An aliquot (0·5 ml) of each sample was vortexed with 2 ml acetonitrile and 10 μg p-chlorodisopyramide (internal standard). The mixture was centrifuged and 2 ml of supernatant was evaporated to dryness under a stream of dry nitrogen. The residue was redissolved in 100 μl acetonitrile and 20 μl aliquots were analysed by high performance liquid chromatography (Waters Assoc. model 6000A pump with fixed wavelength (254 nM) detector and C18 μBondapak column). A mobile phase of 35% acetonitrile and 65% 0·05 M phosphate buffer (pH = 3·0) was used at a flow rate of 2 ml min^{-1}. The rate of drug uptake into the lungs was calculated as the difference per gram of lung between the rate of entry and exit of drug from the perfused organ. All curves were fitted stepwise to polyexponential equations by non-linear regression analysis and statistical comparisons were made using the Student's t-test.

The uptake of both Qn and Qd is shown in Fig. 1 and was best described by a biexponential equation indicating the presence of at least two components responsible for the accumulation of the drugs in lung. As can be seen, the exponent of the exponential term describing the
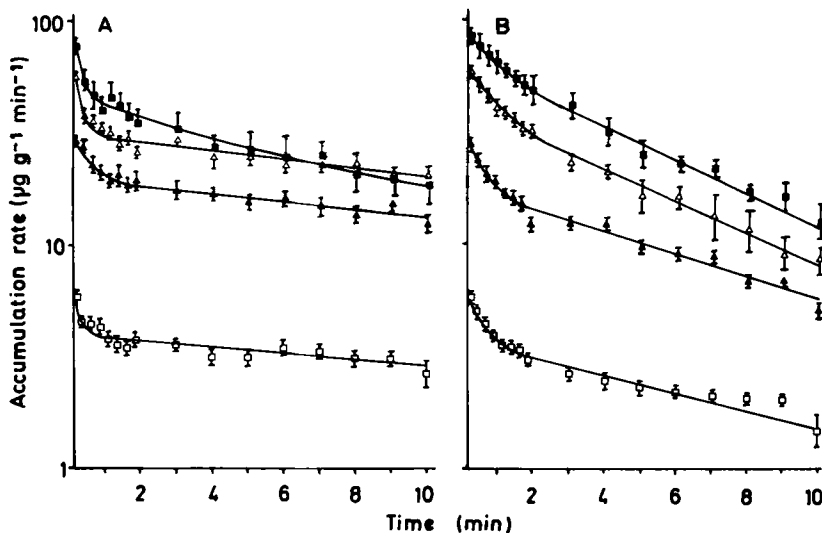
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FIG. 1. Rate of uptake of quinine (A) and quinidine (B) in rat isolated perfused lungs. Data are presented as mean ± s.e.m. (n = 3); □ 1, ▲ 5, △ 10 and ■ 15 μg ml^{-1}. Solid lines show computer predicted line of best fit.

terminal portion of the Qn rate curves was significantly less than that for Qd at all perfusion concentrations, suggesting that the uptake mechanism at the latter times of perfusion differed for the two drugs.

The total amounts of drug accumulated, calculated by integrating the equations from zero to 10 min, are given in Table 1. After 10 min, there was no significant difference in the concentration of Qn and Qd in the lungs at any of the perfusate concentrations used. The ratio of Qn in the lungs at 10 min to that in the perfusate decreased with increasing drug concentration in the perfusion medium (Table 1). For Qd, the tissue to medium ratios were not significantly different.

Fig. 2 illustrates the linearity between the rate of drug infusion and the initial rate of drug uptake into the lungs. These results indicate that no saturable transport processes for either drug were apparent for concentra-

Table 1. Accumulation of quinine and quinidine in isolated perfused rat lung after 10 min.

	Perfusate concn (μg ml^{-1})	Total drug accumulated (μg g^{-1})	$\dfrac{\text{Concn in lung}}{\text{Concn in perfusate}}$
Quinine	1	33·9 ± 6·1*	33·9 ± 6·1
	5	164·7 ± 24·2	32·9 ± 4·8
	10	256·8 ± 32·2	25·7 ± 3·2
	15	292·8 ± 27·5	19·5 ± 1·8
Quinidine	1	26·2 ± 2·2	26·2 ± 2·2
	5	113·4 ± 8·9	22·6 ± 1·8
	10	215·9 ± 17·8	21·6 ± 1·8
	15	334·2 ± 29·2	22·2 ± 1·9

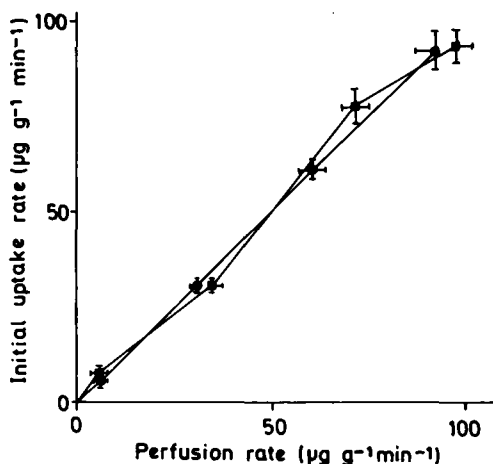* Data expressed as mean ± s.e.m. (n = 3).

FIG. 2. Linear relationship between the rate of drug infusion into the lung preparations and the estimated initial rate of uptake calculated by summing the coefficients of the biexponential equations. For quinine (■), correlation coefficient = 0·99 and regression coefficient = 1·07. For quinidine (●), correlation coefficient = 0·99 and regression coefficient = 0·97. Data as mean ± s.e.m.

Table 2. Distribution of quinine and quinidine in rat blood and lung.

Drug	Concentration Blood (μg ml^{-1})	Lung (μg g^{-1})	Lung/Blood Ratio
Quinine	0·31 ± 0·03*	76·3 ± 11·3	246 ± 36
Quinidine	0·31 ± 0·02	64·3 ± 7·4	207 ± 24

* Data as mean ± s.e.m. (n = 6). Distribution studied 1 h after an intravenous dose of 10 mg kg^{-1}.

tions up to 15 μg ml^{-1}. The observed decrease in the tissue to medium ratios of Qn therefore probably results from a saturable binding process in the lung tissue. Qd, together with a number of other basic amines, have previously been shown to inhibit the binding of chlorphentermine in rat lung subcellular fractions suggesting the presence of common binding sites for these compounds (Minchin et al 1979).

Since the rat perfused lung did not show a quantitative difference in the accumulation of Qn and Qd over 10 min, experiments on the in vivo distribution of these isomers were performed in conscious rats. Qn or Qd was administered via a tail vein (10 mg kg^{-1}) to two groups of animals. After 1 h the rats were killed and blood and lung samples taken for drug analysis. Qn and Qd were extracted by the method of Minchin et al (1980) and determined by h.p.l.c. as above. These results, shown in Table 2, again indicated that Qn and Qd are accumulated to a similar extent with comparable lung/blood distribution ratios.

It can be concluded from the present studies in whole animals and isolated perfused lungs that the extent of accumulation of the isomers Qn and Qd in rats is similar under the experimental conditions used. However, the observed saturability of Qn uptake in lung and the difference in the shape of the rate curves for the two drugs suggest that the mechanism of uptake for Qn and Qd is not the same.

Stereoselectivity in an uptake process is suggestive of the involvement of an active transport mechanism. While the present study did not find evidence for such a process for Qn and Qd in rats, evidence for active transport processes in lung tissue from various species has been suggested for endogenous amines such as 5-hydroxytryptamine and noradrenaline (Strum & Junod 1972; Iwasawa et al 1973) and for basic amines such as amphetamine (Drew & Nicholls 1979), chlorphentermine (Angevine & Mehendale 1980) methadone (Chi & Dixit 1977) and paraquat (Rose et al 1974). Stereoselectivity of uptake has however only been clearly demonstrated for methadone (Chi & Dixit 1977) and mepivacaine (Aberg 1972). The present study also indicates that stereospecific mechanisms for the uptake of compounds may not necessarily be reflected in the extent of their accumulation.

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Comparative effects of leukotriene B_4, prostaglandins I_2 and E_2, 6-keto-PGF$_{1\alpha}$, thromboxane B_2 and histamine on selected smooth muscle preparations

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A number of oxidative metabolites of arachidonic acid are synthesized and released during various inflammatory and hypersensitivity reactions. Among them, there are the prostaglandin endoperoxides which are unstable and rapidly transformed to the various prostaglandins and to the thromboxanes. Other compounds are formed through the action of the platelet lipoxygenase. Recently, the leukotrienes (LTs), a newly discovered group of metabolites (Borgeat & Samuelsson, 1979a, 1979b) formed in polymorphonuclear leukocytes by a lipoxygenase, have been identified as the major chemical bioactive components of Slow Reacting Substance of Anaphylaxis (SRS-A) (Murphy et al 1979; Hammarstrom et al 1979; Samuelsson et al 1980). The LTs are characterized by a conjugated triene structure and are produced through series of enzymatic reactions involving a 5-hydroperoxyeicosatetraenoic acid and an unstable intermediate named LTA_4. LTA_4 could be transformed into LTB_4 or LTC_4 which could undergo another transformation into LTD_4 or SRS-A (for a review, see Sirois & Borgeat 1980). As part of a project designed to evaluate the biological significance of the leukotrienes in hypersensitivity reactions, these experiments were done to compare the activity of selected metabolites of arachidonic acid and of histamine in various smooth muscle preparations.

Smooth muscle preparations: Rat stomachs were obtained from albino animals, prepared according to Vane (1957) and cut in 3–4 cm strips; the guinea-pig and rat ileum and the guinea-pig duodenum were prepared

according to the technique published by the Department of Pharmacology of the University of Edinburgh; the rat and guinea-pig ascending and descending colon were trimmed free from mesentery and prepared according to Gagnon & Sirois (1972); the rat and guinea-pig oesophagus were removed together with the lungs and trachea, dissected free from fat and cut to 2–3 cm; the guinea-pig and rabbit aorta and trachea were cut spirally so as to produce strips of 3–4 × 30 mm; the guinea-pig pulmonary vein was cut open longitudinally; the guinea-pig and rabbit lung parenchymal strips (3 × 3 × 30 mm) were prepared from the edges of the lobes; the chick rectum was trimmed free from fat and cut in 2 cm pieces. Tyrode solution bubbled with air was used with intestinal smooth muscles and Krebs solution bubbled with 5% CO_2 in oxygen with other preparations.

Superfusion technique: After dissection, three smooth muscles were fixed to the bottom of three baths in cascade and to Grass FTO3C isometric transducers and were superfused with either Tyrode or Krebs solution at 37 ° (5 ml min⁻¹). The agonists were injected as a bolus (approx. 50 µl) in the superfusing fluid and the responses of the tissues were recorded on a Grass polygraph.

Drugs used: Histamine dihydrochloride was purchased from Sigma Chem. Co. Prostaglandins I_2 and E_2, 6-keto-PGF$_{1\alpha}$ and thromboxane B_2 were supplied as a generous gift by Dr J. E. Pike, Upjohn Co., Kalamazoo. Leukotriene B_4 was prepared from human polymorphonuclear leukocytes as described by Sirois et al (1980). In brief, the cells were incubated for 4 min in the presence of arachidonic acid (50 µg ml⁻¹) and ionophore A23187 (10 µg ml⁻¹). The lipids were extracted with ether at pH 3 and fractionated by silicic acid

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