A technique for studying drug absorption from the lung in man

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Many bronchodilator drugs are given from pressurised aerosols or by wet nebulisation. It has been shown that a large fraction of an 'inhaled' dose is swallowed (Blackwell, Conolly, Davies & Dollery, 1970 ; Evans, Paterson, Shenfield & Walker, 1972). In order to determine the fate of the small portion reaching the lung, drugs have been administered directly into the lung at diagnostic bronchoscopy in patient volunteers. A thin catheter is threaded down the bronchoscope to a basal bronchus, and a solution of labelled drug is injected. Studies have been performed in four patients, two with disodium cromoglycate (DSCG) (1 mg), and two with salbutamol (0·2 mg).

The plasma picture following bronchoscopic administration showed that both drugs were rapidly absorbed from the lung. In the case of DSCG, 33% and 46% of the dose was recovered from the urine in 24 h, compared with 0·2% seen after oral dosage (Walker, Evans, Richards & Paterson, 1972a). All the recovered radioactivity was unchanged compound. With salbutamol, 24 h recoveries were 80% and 88% of the dose. Metabolite accounted for 27% and 40% of these recoveries. This compares with oral administration, when as much as 60% of the urinary radioactivity was metabolite (Walker, Evans, Richards & Paterson, 1972b).

These results confirm that using standard inhalers only a small proportion of the dose reaches the lung.

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The pharmacokinetics of rimiterol in asthmatic patients

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Rimiterol hydrobromide (erythro-[3,4,dihydroxyphenyl] [2-piperidyl]methanol hydrobromide) is one of a new series of sympathomimetic amines cyclised about the alpha carbon. It has been shown to be equipotent with isoprenaline as a bronchodilator, when given by inhalation (Shenfield & Paterson, 1973), but has considerably less cardiovascular activity (Griffin & Turner, 1971).

The pharmacokinetics of ^{14}C-rimiterol following administration orally, by inhalation and via a bronchoscope, have been studied in asthmatic patients.

After oral administration (10 mg, four patients) peak plasma levels of radioactivity of 210–395 nM were seen 1–5 h after dosing. Very little free rimiterol could be detected in the plasma, and there was no change in spirometric measurements following administration. Analysis of 0–24 h urine indicated that 1·0–2·1% of the radioactivity was free rimiterol, 1·9–3·7% free 3-0-methyl rimiterol, 41·8–55·8% conjugated rimiterol, and 22·6–31·3% conjugated 3–0-methyl rimiterol.

Four patients received the drug from a pressurized aerosol (0·40–0·56 mg) and here improvement in spirometric measurements occurred within 5 min. This did not correlate

with the total plasma radioactivity which reached a peak level of 8·7–28·1 nM, 2–5 h after dosing. The pharmacokinetic pattern was similar to that observed after oral administration, suggesting that as previously reported for isoprenaline (Blackwell, Conolly, Davies & Dollery, 1970), and salbutamol (Evans, Paterson, Richards & Walker, 1971), most of a pressurized aerosol dose is swallowed.

Rimiterol (0·45–0·48 mg) given via a bronchoscope to three patients was well absorbed, giving rise to peak plasma levels of 16·5–31·2 nM, 5 min–2·5 h after dosing. The majority of the plasma radioactivity in early samples was due to free rimiterol, and free 3-0-methyl rimiterol was also detectable. The plasma picture was reflected in the pattern of urinary excretion, where 17·3–22·0% of the radioactivity was due to free rimiterol, 13·5–14·4% was free 3-0-methyl rimiterol, 5·3–7·9% was conjugated rimiterol, and 39·6–50·8% conjugated 3-0-methyl rimiterol.

Thus the pattern of metabolism of rimiterol after oral administration differs from that seen after administration into the lung, in two respects: firstly, the extent of 3-0-methylation, and secondly, the pattern of conjugation.

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Preliminary observations on the human pharmacology of I.C.I. 66082 in normal volunteers

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I.C.I. 66082, 4-(2-hydroxy-3-isopropylaminopropoxy) phenyl acetamide is a cardioselective β-adrenoceptor blocking agent in animals, without intrinsic sympathomimetic or membrane action (Barrett, Carter, Fitzgerald, Hull & Le Count, 1973; Harry, Knapp & Linden, 1973; Hainsworth, Karim & Stoker, 1973).

Pilot studies were used to assess dosage. Hourly observations with oral 200 mg I.C.I. 66082 or 80 mg propranolol then indicated the maximum adrenergic inhibition obtained (Table 1).

TABLE 1. *Heart rate response (H.R., mean ± S.E. mean, n = 4)*

Maximum inhibition of:	I.C.I. 66082 (200 mg) Control	I.C.I. 66082 (200 mg) Drug	Propranolol (80 mg) Control	Propranolol (80 mg) Drug
*H.R. supine	53 ± 5·2	51 ± 2·6	54 ± 3·9	52 ± 4·6
p	> 0·20		> 0·20	
H.R. after tilting 80° 1 min.	69 ± 7·6	58 ± 5·0	69 ± 6·6	61 ± 5·7
p	> 0·025		< 0·02	
Tilt tachycardia	16 ± 2·7	8 ± 2·7	15 ± 4·1	9·0 ± 3·1
p	< 0·001		< 0·05	
H.R. end valsalva	94 ± 13·3	66 ± 4·7	96 ± 3·0	73 ± 3·8
p	< 0·025		< 0·20	
Val. tachycardia	25 ± 10·2	4·3 ± 2·0	27 ± 6·3	12·0 ± 3·3
p	< 0·20		< 0·10	
H.R. end exercise (150 watts)	119 ± 3·4	97 ± 5·0	116 ± 4·0	101 ± 2·5
p	< 0·02		< 0·02	
Ex. tachycardia	49 ± 7·6	31 ± 4·9	47 ± 4·9	32 ± 1·8
p	< 0·05		< 0·10	
Isoprenaline dose to give increase 20/min.	2·7 ± 0·7	**29 ± 10·3	4·0 ± 0·5	**103 ± 22·7
p	*** < 0·10		< 0·02	

*H.R. = heart rate.
**difference between dose of isoprenaline after I.C.I. 66082 and propranolol significant, $p < 0·02$.
***p calculated on log values < 0·02
p values, two tail.