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ABSORPTION OF DRUGS BY THE LUNG

GILLIAN M. SHENFIELD,[1] MARION E. EVANS[2] & J.W. PATERSON[3]
Asthma Research Council Clinical Pharmacology Unit, Department of Medicine, Cardiothoracic Institute, London SW3 6HP

1 Ten patients undergoing diagnostic bronchoscopy had radioisotopically labelled drugs put directly into their bronchi; two received sodium cromoglycate, two salbutamol, three salmefamol and three rimiterol.

2 All four drugs were rapidly absorbed but higher peak plasma levels per unit dose were seen with sodium cromoglycate and salbutamol than with the other two drugs.

3 It is suggested that the lung metabolizes salmefamol and rimiterol but does not metabolize salbutamol or sodium cromoglycate.

Introduction

It has been previously shown that when drugs are given by pressurized aerosol the majority of the dose is swallowed (Paterson, Conolly, Davies & Dollery, 1968; Evans, Paterson, Richards & Walker, 1971; Blackwell, Briant, Conolly, Davies & Dollery, 1973). This swallowed fraction dominates the pharmacokinetic picture making it difficult to assess the rôle of the lung in absorption and metabolism.

If salbutamol is given by wet aerosol a different pharmacokinetic picture is seen. There is an early peak plasma level with little metabolism of the drug (Shenfield, Evans & Paterson, 1974). It has been suggested that this early absorption represents that portion of the drug reaching the lungs. To obtain more information on how the lung absorbed and metabolized drugs we therefore administered drugs directly into the lung at diagnostic bronchoscopy.

Methods

Table 1 lists the patients studied giving their diagnoses and the drug they each received. All were in hospital for diagnostic bronchoscopy and readily agreed to being given a small dose of radioactive drug. Two patients were given [^{14}C]-disodium cromoglycate (disodium salt of 1,3-bis(2-carboxy-chromon-5-yloxy)-2-hydroxy propane), two [^{3}H]-salbutamol (2-*t*-butylamino-1-[4-hydroxy-3-hydroxymethyl]-phenyl-ethanol), three [^{3}H]-salmefamol (*p*-methoxyphenyl-1[4-hydroxy-3-hydroxy-methyl]-phenyl-ethanol), and three [^{14}C]-rimiterol (erythro-2-piperidine-methanol-α-[3,4-dihydroxy-phenyl]-hydrobromide).

They all received routine premedication with Omnopon (20 mg), atropine (0.6 mg) and were fasted from midnight. They were anaesthetized with intravenous thiopentone and scoline. During the procedure they were given oxygen. Once they were anaesthetized an indwelling venous cannula (Braunula) was inserted and a blood sample (5 ml) was taken. The surgeon performed his investigation in the normal way, taking a biopsy if indicated. As soon as he had finished (usually about 5 min) a thin plastic catheter (Wallace suction catheter) was threaded down the bronchoscope and wedged in a basal bronchus. The radioactively labelled drug, contained in 1 ml of solution, was then injected down the catheter, washed through with normal saline (2 ml) and then blown through with air (5 ml) to ensure as peripheral a site of deposition as possible. Blood (5 ml each sample) was taken as soon as possible (within 2 min) and then at 5, 10, 20, 30, 45 and 60 min, and at 1, 1.5, 2, 3, 4, 5, 6 and 8 hours.

Present addresses
[1] Diabetic and Dietetic Department, Royal Infirmary, Edinburgh
[2] Department of Pharmacology, Faculty of Medicine, University of British Columbia, Vancouver, Canada
[3] Department of Pharmacology, Perth Medical Centre, University of Western Australia, 6009 Western Australia

Patients were often in hospital for only 24 h but in all cases a 24 h urine collection was made and where possible it was collected for longer.

Chemical methods

All the radioactive samples were counted in a Packard Tri-Carb liquid scintillation spectrometer (model no. 3375).

Samples of urine (0.5 ml) were counted in Insta-Gel (9 ml). Whole blood was collected in heparinized tubes, spun at 2000 rev/min for 10 min and aliquots of plasma (2 ml) counted in Insta-Gel (18 ml). All samples were analysed in duplicate. For the tritiated compounds (salbutamol and salmefamol) efficiency was determined by the automatic external standard ratio (AES) method. For the ^{14}C compounds (rimiterol and disodium cromoglycate) efficiency was determined by the 'channels ratio method'.

Samples were analysed for the presence of free drug and metabolite by the methods previously described; disodium cromoglycate (Walker, Evans, Richards & Paterson, 1972); salbutamol (Evans, Walker, Britten & Paterson, 1973); salmefamol (Evans, Shenfield & Paterson, 1974a) and rimiterol (Evans, Shenfield, Thomas, Walker & Paterson, 1974b).

Results

Side-effects were not assessed since both pulse rate and blood pressure were changing rapidly as the patients recovered from the anaesthetic. At the doses given changes in pulse rate would not be anticipated.

Results for one patient from each drug group are shown in Figure 1 (disodium cromoglycate), Figure 2 (salbutamol), Figure 3 (salmefamol), and Figure 4 (rimiterol). With all four drugs there is an early peak plasma level within 10 min of drug administration. In the case of disodium cromoglycate this is entirely due to free drug. With the other compounds the proportion of free drug is as follows: salbutamol 87% (86-88%), salmefamol 85% (74.5-100%) and rimiterol 82.3% (79.4-86%).

Table 2 gives the first peak plasma level of total radioactivity expressed firstly as nmol litre^{-1} and, in the last column, as nmol litre^{-1} μmol^{-1} of dose. The first peak plasma level per unit dose is 33.9 nmol litres^{-1} μmol^{-1} (19.2-48.7 nmol litres^{-1} μmol^{-1}) for disodium cromoglycate; 44 nmol litre^{-1} μmol^{-1} (26.8-61.1 nmol litre^{-1} μmol^{-1}) for salbutamol; 9.9 nmol litre^{-1} μmol^{-1} (8.3-12.2 nmol litre^{-1} μmol^{-1}) for salmefamol; and 14.0 nmol litre^{-1} μmol^{-1} (10.3-20.8 nmol litre^{-1} μmol^{-1}) for rimiterol: that is the initial peak level per unit dose is higher for disodium cromoglycate and salbutamol than for the other two drugs.

Figure 1 shows that after the initial peak the plasma level of disodium cromoglycate declines rapidly, and Figure 2 shows that, with salbutamol, both plasma total radioactivity and plasma-free drug decline rapidly. Figures 3 and 4 show that, in contrast, after salmefamol and rimiterol the plasma level is maintained and a second peak occurs. This second peak is at a mean of 34 min (24-45 min) for salmefamol, and 2.2 h (2.0-2.5 h) for rimiterol.

Table 3 expresses total plasma radioactivity at a given time after administration as a percentage of the first peak plasma level. It can be seen that this falls rapidly for disodium cromoglycate and salbutamol, but even at 4 h is still relatively high for the other two drugs.

The 24 h urinary recovery for all the patients and also the percentage of the urinary radioactivity as free (unchanged) drug are given in Table 4. Disodium cromoglycate is not metabolized. There is a much higher percentage excretion of free drug with salbutamol 62.2% (57.8-66.6%) than for the other two drugs: salmefamol 13.8% (6.4-24.2%) and rimiterol

Table 1 Details of patients studied

Patient	*Age (years)*	*Diagnosis*	*Drug*	*Dose (mg)*
J.H.	60	Carcinoma of bronchus	Disodium cromoglycate	1.00
R.M.	29	Foreign body in bronchus	Disodium cromoglycate	1.00
F.H.	59	Carcinoma of bronchus	Salbutamol	0.22
R.C.	62	Carcinoma of bronchus	Salbutamol	0.2
Z.P.	75	Haemoptysis	Salmefamol	0.18
P.S.	55	Carcinoma of breast	Salmefamol	0.18
E.J.	63	Carcinoma of bronchus	Salmefamol	0.18
R.C.	59	? Carcinoma of bronchus	Rimiterol	0.5
A.D.	22	Sarcoidosis	Rimiterol	0.5
R.N.	49	Carcinoma of bronchus	Rimiterol	0.48

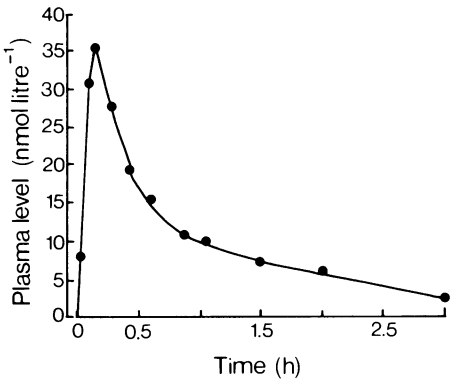

Figure 1 Patient J.H. Plasma levels after administration of [^{14}C]-disodium cromoglycate (1 mg, 1.67 μCi) via a bronchoscope.

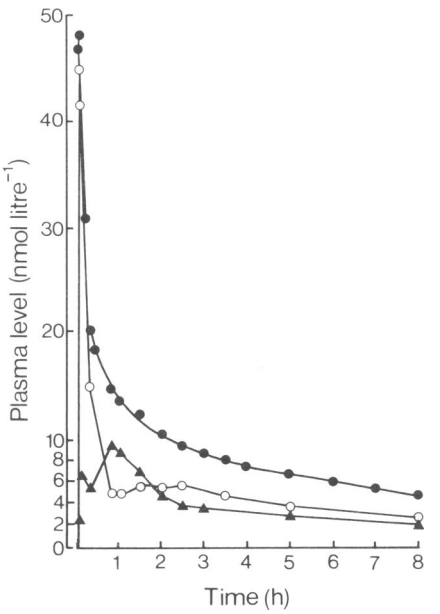

Figure 2 Patient R.C. Plasma levels after administration of [^{3}H]-salbutamol (0.19 mg, 73.8 μCi) via a bronchoscope (● total radioactivity; ○ salbutamol; ▲ metabolite of salbutamol).

20.1% (17.3-22.3%). In patient E.J. 4.7% of the original dose was recovered from the faeces. Figure 5 illustrates the pattern of urinary excretion after rimiterol was administered to patient A.D.

Figure 5 gives more detailed analysis of the urinary excretion for rimiterol. Fourteen per cent (13.5-14.4%) of the urinary radioactivity was in the form of free 3-*O*-methyl-rimiterol, 45% (39.6-50.8%) as sulphated 3-*O*-methyl-rimiterol,

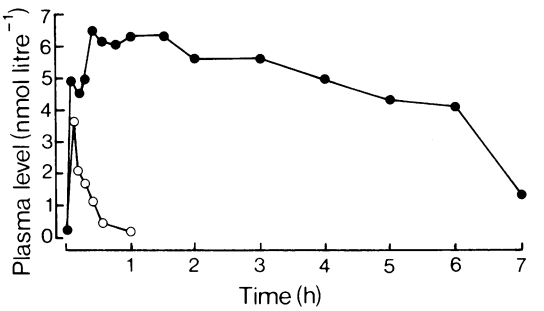

Figure 3 Patient Z.P. Plasma levels after administration of [^{3}H]-salmefamol (0.18 mg, 26.3 μCi) via a bronchoscope (● total radioactivity; ○ salmefamol).

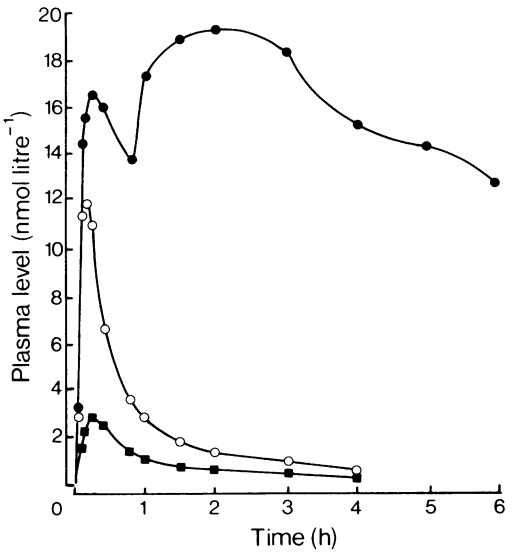

Figure 4 Patient A.D. Plasma levels after administration of [^{14}C]-rimiterol (0.48 mg, 48 μCi) via a bronchoscope (● total radioactivity; ○ rimiterol; ■ 3-*O*-methyl-rimiterol).

and 14.2% (11.6-17.0%) as glucuronides most of which were of 3-*O*-methyl-rimiterol. Thus in contrast to the excretion pattern after oral and aerosol administration (Evans *et al.*, 1974b), well over half the urinary radioactivity is due to the 3-*O*-methyl derivative of rimiterol.

Discussion

Enna & Schanker (1972) investigated absorption of drugs from the rat lung and found that absorption occurred much more rapidly than from the gastro-intestinal tract. With most compounds

Table 2 Doses and peak plasma levels of radioactivity

Patient	*Drug*	*Dose (μ mol)*	*First peak plasma level of radioactivity (nmol litre^{-1})*	*Peak plasma level of radioactivity per unit dose (nmol litre^{-1} μmol^{-1})*
R.M.	Disodium cromoglycate	1.92	54.6	48.7
J.H.	Disodium cromoglycate	1.92	34.6	19.1
F.H.	Salbutamol	0.89	23.9	26.8
R.C.	Salbutamol	0.79	48.3	61.1
Z.P.	Salmefamol	0.54	5.0	9.3
P.S.	Salmefamol	0.54	4.5	8.3
E.J.	Salmefamol	0.54	6.6	12.2
R.C.	Rimiterol	1.6	17.5	10.9
A.D.	Rimiterol	1.6	16.5	10.3
R.N.	Rimiterol	1.5	31.2	20.8

Table 3 Mean plasma levels (range in brackets) at different times after dosing

	Total plasma radioactivity as % of first peak level at the following times after dosing				
	1 h	*2 h*	*4 h*	*8 h*	*24 h*
Disodium cromoglycate	26.0 (24-28)	13.3 (9.5-17.0)	5.25 (5-5.5)	– –	– –
Salbutamol	38.5 (28-49)	30.5 (21-40)	21.4 (15-28)	18.0 (10-26)	7.5 (4-11)
Salmefamol	111.0 (96-126)	98.3 (90-113)	77.3 (65-100)	38.0 (26-44)	19.0 (13-27)
Rimiterol	87.0 (67-105)	99.0 (72-117)	85.0 (64-99)	50.3 (35-61)	4.2 (3.4-5.7)

Table 4 Urinary recovery of the drugs studied

Patient	*Drug*	*Dose (mg)*	*% dose recovered in urine in 24 h*	*% 24 h urinary radioactivity as free drug*
R.M.	Disodium cromoglycate	1.0	33.3	100
J.H.	Disodium cromoglycate	1.0	46.1	100
F.H.	Salbutamol	0.22	90.8	66.6
R.C.	Salbutamol	0.2	87.4	57.8
Z.P.	Salmefamol	0.18	50.7	10.8
P.S.	Salmefamol	0.18	54.7	24.2
E.J.	Salmefamol	0.18	66.9	6.4
R.C.	Rimiterol	0.5	59.5	21.1
A.D.	Rimiterol	0.5	67.5	17.3
R.N.	Rimiterol	0.48	77.9	22.3

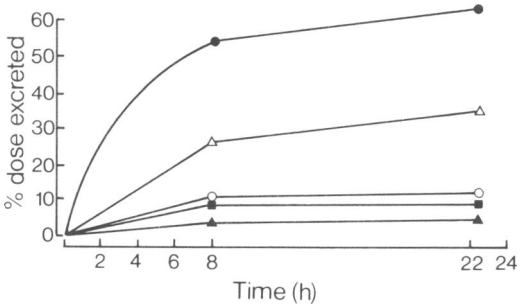

Figure 5 Patient A.D. Urinary excretion after administration of [^{14}C]-rimiterol (0.48 mg, 48 μCi) via a bronchoscope (● total radioactivity; ○ rimiterol; ▲ conjugated rimiterol; ■ 3-*O*-methyl-rimiterol; △conjugated 3-*O*-methyl-rimiterol).

studied the absorption rate constants were roughly related to chloroform-water partition co-efficient, i.e., the greater the co-efficient, the more rapid was the absorption rate. However, some exceptions to this general relationship were seen among drugs of very low lipid solubility. Some of these were unexpectedly rapidly absorbed and among this group the rate of absorption was inversely proportional to the molecular weight. The authors felt that these findings could be explained in terms of diffusion of solutes through aqueous membrane pores of various diameters. They thought that there may be at least three different populations of pore size involved in the absorption of molecules as small as urea (molecular weight 60) and as large as dextran (molecular weight 5000).

The lung is also capable of metabolizing drugs. Leary & Smith (1970) demonstrated that the lung could convert angiotensin I to angiotensin II. Uehleke & Hellmer (1972) showed that cat lungs are capable of dealkylation and *N*-oxidation transformations, and it is also known that human lungs contain catechol - *O* - methyl - transferase – COMT (Paterson *et al.*, 1968).

Briant, Blackwell, Williams, Davies & Dollery (1973) studied the metabolism of isoprenaline, isoetharine and terbutaline in the isolated perfused dog lung. All were rapidly absorbed and both isoprenaline and isoetharine were extensively *O*-methylated. Terbutaline, a resorcinol and hence resistant to COMT, was not metabolized in this system.

Our results confirm and expand these findings. The striking feature is the difference between disodium cromoglycate and salbutamol and the other two drugs. All four drugs are rapidly absorbed by the lung but disodium cromoglycate and salbutamol have higher initial peak plasma levels per unit dose and these decline rapidly. Disodium cromoglycate is not metabolized and over 60% of urinary radioactivity excreted after salbutamol is in the form of unchanged drug. In contrast, salmefamol and rimiterol have lower early peaks and prolonged plasma levels suggesting a delay in absorption and/or metabolism. The comparatively low early level suggests that this delay is occurring in the lungs. Less than 25% of the urinary radioactivity is excreted as the free drug. This pattern is similar to that seen when isoprenaline and isoetharine are administered via an endotracheal tube (Blackwell *et al.*, 1973; Williams, Briant, Dollery & Davies, 1974). With both salmefamol and rimiterol there is a second peak plasma level which occurs earlier with salmefamol.

The nature of the 'delay' in the lungs remains speculative. It is well-known that the lungs can take up drugs. Thus Junod (1972) showed that [^{14}C]-imipramine was accumulated by rat lungs. A great deal is known about 'uptake mechanisms' for catecholamines. These have recently been reviewed by Gillespie (1973) and Iversen (1973). Uptake$_1$ is presynaptic and seems to be specific for the endogenous catecholamines. Uptake$_2$ is extraneuronal, principally into smooth muscle and may be a means of inactivating catecholamines.

Axelrod, Weil-Malherbe & Tomchick (1959) found in cats that, after intravenous injection, tritiated adrenaline was rapidly taken up by the tissues. After 2 min, concentrations of 3-*O*-methyladrenaline (metanephrine) were higher in most tissues than those of adrenaline, indicating rapid *O*-methylation. The lung was one of the organs in which it was present in relatively high concentrations. Masek, Svec, Dlabac & Raskova (1967) using [^{3}H]-noradrenaline showed that it was accumulated in considerable amounts by the lungs. This accumulation was not affected by reserpine or tyramine and was probably extraneuronal. This would correspond to an uptake$_2$ process. Uptake$_2$ is an active process and is rapidly followed by metabolism. The rate of uptake can be altered by inhibiting enzymes such as MAO and COMT (Kalsner, 1969; Gillespie, 1973). Of the synthetic substances similar to adrenaline and noradrenaline, isoprenaline has been shown to be a substrate for uptake$_2$ (Callingham & Burgen, 1966), and for COMT. It has been shown that the catecholamines isoprenaline and isoetharine behave in the same way as rimiterol when put into the lung (Blackwell *et al.*, 1973; Williams *et al.*, 1974). All are substrates for COMT and thus for uptake$_2$. It could be that the early peak plasma levels seen represent that proportion of the drug immediately absorbed. The rest is taken up by the lung, possibly by uptake$_2$, and then metabolized by COMT. This is then slowly released, hence

maintaining the plasma level. This view would be supported by the high proportion of the 3-*O*-methyl derivative of rimiterol in the urine.

All the catecholamines may be metabolized by COMT. Salbutamol is not a catecholamine and hence not a substrate for COMT. The tertiary butyl group protects it from the action of MAO (disodium cromoglycate as an unrelated compound is also not metabolized by COMT or MAO). Thus if uptake$_2$ is related to metabolism neither salbutamol nor disodium cromoglycate would be expected to be taken up by the lungs. This would account for the immediate absorption producing a high early peak plasma level and a rapid decline with no second peak. It is also consistent with 60% of urinary radioactivity being free salbutamol.

Salmefamol is not a catecholamine and hence not a substrate for COMT. Like salbutamol it is not a substrate for MAO, yet its plasma pattern after lung absorption is like that of rimiterol and isoprenaline. After oral administration, Evans *et al.* (1974a) found very little free drug to account for its pharmacological effect and postulated that it underwent demethylation to produce AH 4553. If this does occur then it might also occur in the lung. There is no reason to assume that COMT and MAO are the only enzymes associated with uptake. The lung contains significant amounts of demethylating enzymes (Uehleke & Hellmer, 1972) and could metabolize salmefamol. If such metabolism occurs it might be linked to uptake and hence explain the present findings.

The present method is not without problems since it is not known whether anaesthetics or disease states such as carcinoma alter the absorptive properties of the lungs. In addition, the exact site of absorption is not known although it must be distal to the basal bronchus. The technique is, however, useful and suggests that the lung absorbs drugs well. It also suggests that it metabolizes some drugs. To verify our hypothesis about the relationship of metabolism to uptake$_2$ several things need to be demonstrated. Firstly, the metabolite of salmefamol needs to be identified. Secondly, it should be shown *in vitro* that salmefamol and rimiterol are substrates for uptake$_2$ and that this relates to their metabolism. Finally it should be shown *in vitro* that disodium cromoglycate and salbutamol are not substrates for uptake$_2$.

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Reprint requests to J.W.P., Department of Pharmacology, Perth Medical Centre, University of Western Australia, 6009 Western Australia.

References

AXELROD, J., WEIL-MALHERBE, H. & TOMCHICK, R. (1959). The physiological disposition of [H^3]-epinephrine and its metabolite metanephrine. *J. Pharmac. exp. Ther.*, 127, 251-256.

BLACKWELL, E.W., BRIANT, R.H., CONOLLY, M.E., DAVIES, D.S. & DOLLERY, C.T. (1974). Metabolism of isoprenaline after aerosol and direct intrabronchial administration in man and dogs. *Br. J. Pharmac.*, **50**, 587-591.

BRIANT, R.H., BLACKWELL, E.W., WILLIAMS, F.M., DAVIES, D.S. & DOLLERY, C.T. (1973). The metabolism of sympathomimetic bronchodilator drugs by the isolated perfused dog lung. *Xenobiotica*, **3**, 787-799.

CALLINGHAM, B.A. & BURGEN, A.S.V. (1966). The uptake of isoprenaline and noradrenaline by the perfused rat heart. *Mol. Pharmac.*, **2**, 37-42.

ENNA, S.J. & SCHANKER, L.S. (1972). Absorption of drugs from the rat lung. *Am. J. Physiol.*, **223**, 1227-1231.

EVANS, M.E., PATERSON, J.W., RICHARDS, A.J. & WALKER, S.R. (1971). Pharmacokinetics of inhaled salbutamol in asthmatic patients. *Br. J. Pharmac.*, **43**, 466P-467P.

EVANS, M.E., SHENFIELD, G.M. & PATERSON, J.W. (1974a). The clinical pharmacology of salmefamol. *Br. J. clin. Pharmac.*, **1**, 391-397.

EVANS, M.E., WALKER, S.R., BRITTAIN, R.T. & PATERSON, J.W. (1973). The metabolism of salbutamol in man. *Xenobiotica*, **3**, 113-120.

GILLESPIE, J.S. (1973). Uptake of noradrenaline by smooth muscle. *Br. med. Bull.*, **29**, 136-141.

IVERSEN, L.L. (1973). Catecholamine uptake processes. *Br. med. Bull.*, **29**, 130-135.

JUNOD, A.F. (1972). Accumulation of [^{14}C]-imipramine in isolated perfused rat lungs. *J. Pharmac. exp. Ther.*, **183**, 182-187.

KALSNER, S. (1969). Mechanism of hydrocortisone potentiation of responses to epinephrine and norepinephrine in rabbit aorta. *Circulation Res.*, **24**, 383-395.

LEARY, W.P. & SMITH, U. (1970). *In situ* perfusion of isolated rat lung. *Life Sci.*, **9**, Part 1, 1321-1326.

MASEK, K., SVEC, P., DLABAC, A. & RASKOVA, H. (1969). The accumulation of [^{3}H]-noradrenaline by the lung. *Eur. J. Pharmac.*, **5**, 374-378.

MINATOYA, H., LANDS, A.M. & PORTMANN, G.A. (1965). Absorption and elimination profile of isoproteronol. I. Anaesthetised dogs. *J. pharm. Sci.*, **54**, 968-972.

PATERSON, J.W., CONOLLY, M.E., DAVIES, D.S. & DOLLERY, C.T. (1968). Isoprenaline resistance and the use of pressurised aerosols in asthma. *Lancet*, **ii**, 426-429.

SHENFIELD, G.M., EVANS, M.E. & PATERSON, J.W. (1974). The effect of different nebulisers with and without intermittent positive pressure breathing on the absorption and metabolism of salbutamol. *Br. J. clin. Pharmac.*, **1**, 295-300.

UEHLEKE, H. & HELLMER, K.H. (1972). *Lung metabolism of drugs.* Symposium on Extrahepatic Drug Metabolism, pp. 11-12. London: Royal College of Physicians.

WALKER, S.R., EVANS, M.E., RICHARDS, A.J. & PATERSON, J.W. (1972). The fate of [^{14}C]-disodium cromoglycate in man. *J. Pharm. Pharmac.*, **24**, 525-531.

WILLIAMS, F.M., BRIANT, R.H., DOLLERY, C.T. & DAVIES, D.S. (1974). The influence of the route of administration on urinary metabolites of isoetharine. *Xenobiotica*, **4**, 345-353.

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