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First pass uptake of ^{14}C-propranolol by the lung

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ABSTACT Uptake of ^{14}C-propranolol by the lungs during a single passage through the pulmonary circulation was measured in ten patients at cardiac catheterisation. Mean lung uptake of propranolol was 75% in seven patients who were not previously taking the drug and 33% in three patients who were taking it as regular oral treatment. Lung uptake of propranolol in man is therefore considerable and is partly saturable by normal oral doses. This may alter the dose response relation for propranolol and a wide range of other drugs when given intravenously.

The method used to study lung uptake is simple and might be suitable for studies of endothelial cell function in disease.

Many compounds are taken up by the lung from the circulation (Brown, 1974). This property of the lung has been little studied in man, although it may be important in modifying the circulating levels of drugs. This is especially true when drugs acting on the heart are given intravenously, since lung uptake may result in unpredictable drug levels in coronary artery blood resulting in equally unpredictable changes in heart rate or rhythm. We have therefore measured lung uptake of ^{14}C-propranolol in man to find out the extent to which this occurs during the first passage through the pulmonary circulation and to establish whether the process is saturable at normal therapeutic doses. These studies suggest that the lung has an important first pass effect on circulating drug levels.

Methods

Fifteen measurements of lung uptake of propranolol were made in ten patients. All were undergoing routine cardiac catheterisation for ischaemic heart disease. All patients gave fully informed consent to the study, which was approved by the hospital ethics committee. Patient details are given in table 1. No patient had any evidence of lung disease or pulmonary oedema on physical

Table 1 *Details of 10 patients taking part in study*

Patient	*Age*	*Sex*	*Cardiac index l/min/m²*	*^{14}C-propranolol*	
				Lung uptake %	*Arterial concentration ng/ml*
Group 1					
1	63	M	2·3	83	35
2	53	M	1·6	79	25
3	60	M	2·6	70	77
4	56	M	2·7	56	128
				82	58
5	45	M	2·1	47	134
				87	42
6	52	F	2·1	80	88
				83	48
7	46	M	1·2	83	45
			Mean ± SD	75 ± 13·3	68 ± 38
Group 2 (oral propranolol)					
8	43	F	2·4	47	130
9	46	M	1·7	30	258
				42	150
10	50	F	2·9	15	420
				29	250
			Mean ± SD	32·6 ± 12·4	242 ± 115

examination or chest radiograph. Measurements were made with catheters positioned in the main pulmonary artery and ascending aorta. Each patient had received amylobarbitone 200 mg intravenously as premedication 30–60 minutes before the procedure and 5000 units of heparin intravenously at the beginning of the catheter investigation. The patients were divided into two groups. Group 1 contained seven patients who had never previously received propranolol; ten measurements of lung uptake were made. Group 2 contained three patients who were taking regular oral propranolol 40 mg three or four times daily; five measurements of lung uptake were made. Each patient in group 2 had taken an oral dose of propranolol 4–6 hours before the investigation.

Lung uptake was measured by comparing the concentration of propranolol with an intravascular marker after a single passage through the pulmonary circulation. A mixture of ^{14}C-propranolol 0·5 mg (ICI, specific activity 14·66 μCi/mg) and indocyanine green (ICG) 2·5 mg (Hynson, Westcott, and Dunning Inc) total volume 1 ml were injected into the dead space of the pulmonary artery catheter. The mixture was flushed in as a rapid bolus by injection of 10 ml 5% dextrose through the catheter. Immediately before the bolus injection 15 ml of aortic blood was sampled, and a further 15 ml was withdrawn from the moment of the bolus injection at a constant rate of 1 ml/s over 15 seconds. The average time from injection to recirculation determined from a semilogarithmic replot of the washout phase of the ICG indicator dilution curves obtained in other patients is 15 seconds. The post-bolus 15 second collection, therefore, samples blood containing the first pass outflow of propranolol and ICG from the lung. The blood samples were transferred to lithium heparin tubes, centrifuged for 10 minutes at 3000 rpm, and separated. The plasma was used for estimation of ^{14}C-propranolol and ICG. Plasma from the pre-injection aortic sample was used as a blank and for construction of calibration curves. Blood was also taken during the catheterisation procedure for measurement of oxygen content of mixed venous and aortic blood, and for estimation of the haematocrit.

ICG was chosen as an intravascular marker because it is used routinely in measuring cardiac output. In a comparison in dogs between ICG and ^{125}I-albumin the two intravascular markers behaved identically.

Lung uptake of propranolol was calculated by comparing the ratio of drug to dye injected with their ratio in the first pass washout blood as follows:

$$R_1 = \frac{\text{concentration of } ^{14}\text{C-propranolol injected}}{\text{concentration of ICG injected}}$$

$$R_2 = \frac{\text{concentration of } ^{14}\text{C-propranolol in aortic blood}}{\text{concentration of ICG in aortic blood}}$$

$$\left[1 - \frac{R_2}{R_1}\right] \times 100 = \text{percent uptake of } ^{14}\text{C-propranolol during a single passage through the lungs.}$$

Analytic procedures

ICG was estimated by spectrophotometry at 805 nm in plasma. Aortic plasma taken from the same patient just before the first injection was used as a blank and also for construction of a calibration curve. This was done by adding 5 μl increments of a 1 : 10 dilution of the ICG used in the experiment to 2 ml of aortic blood plasma. The calibration curve was linear over the dose range used. Measurements were made within two hours of the experiment and the results expressed in ng/ml.

^{14}C-propranolol was estimated in plasma by liquid scintillation counting after addition of NE 260 (nuclear enterprises). An external standard was used to monitor counting efficiency, and radioactivity measurements were corrected accordingly. A calibration curve was constructed using standard dilutions of ^{14}C-propranolol in plasma, and this was linear over the range of concentrations encountered. Since propranolol is distributed between plasma and cells in whole blood the plasma concentration was corrected to give the propranolol concentration that would be obtained if all the drug were in the plasma. For this correction the ratio of propranolol in blood to plasma was taken as 0·8. This was shown by Evans *et al* (1973) to be constant over the range of drug concentrations encountered in these experiments. Using this partition constant the measured ^{14}C-propranolol concentration was multiplied by $(1-0{\cdot}44H)/1-H$ (where H is the haematocrit) to give the corrected plasma drug concentration. The correction is necessary to compare the ^{14}C-propranolol level with the plasma ICG concentration. ICG was assumed to be diluted only in plasma and not to be distributed to blood cells. To the extent that this assumption is wrong it will tend to underestimate lung uptake of ^{14}C-propranolol.

Cardiac output in these patients was estimated by the Fick principle using oxygen content of mixed venous and aortic blood and is expressed as the cardiac index in $l/min/m^2$ body surface area. Statistical analysis was performed with Wilcoxon's two sample test.

Results

Results are listed in table 1. Measurements in group 1 (no oral propranolol) show a mean first pass uptake of 75±13·3% (range 47–87%), while those in group 2 show a mean uptake of 33± 12·4% (range 15–47%). This difference is significant ($P<0.01$). Similarly the mean estimated plasma concentration of ^{14}C-propranolol is significantly different between the two groups: 68± 38 ng/ml in group 1 and 242±115 ng/ml in group 2 ($P<0.01$).

Discussion

Lung uptake of propranolol has previously been shown in dogs, rats, and monkeys (Hayes and Cooper, 1971). Our studies confirm that the uptake also occurs in man and show further that the process is rapid and saturable. The rapidity of uptake is not surprising: in the only comparable animal experiments Dollery and Junod (1976) found that uptake of propranolol by an isolated perfused rat lung reached a maximum within five minutes—the shortest perfusion period in their experiments. Propranolol probably shares with other basic lipophilic amines a non-specific uptake on to the endothelial cell membrane with little if any active transport or metabolism. Previous elegant studies with simple radioactively labelled aliphatic amines have indicated similar very rapid uptake by the lungs in man (Gallagher *et al*, 1977) and rabbits (Anderson *et al*, 1974). Patients already taking propranolol showed conspicuously less lung uptake of the intravenous dose. Other evidence that binding sites for the drug can be saturated was obtained in the isolated rat experiments over a range of perfusate concentrations between 0·2 μm and 1 mm (Dollery and Junod, 1976) and although direct comparison with these findings is impossible, it may be relevant that the concentration achieved in the pulmonary artery in the present experiment was within this range.

Our results should be interpreted with caution since we have assumed firstly that all the radioactivity measured is in the form of propranolol rather than its metabolites and secondly that equilibration of the drug between plasma and blood cells is complete. Appreciable metabolism of the drug during a single passage through the lungs is unlikely; there was negligible metabolism by the isolated perfused rat lung in the experiments of Dollery and Junod (1976). In any case if some of the radioactivity measured is in the form of metabolites then the amount of intact drug reaching the systemic circulation is less than our calculations and so the effect of the lungs is greater. The relative rate of uptake of the drug between red cells and the lung is more complex. A peripheral venous injection will allow longer time for contact between blood cells and the drug before the pulmonary circulation is reached. In theory this might result in less drug being available for uptake by the pulmonary circulation and so we may have over-estimated uptake. Nevertheless, most of the drug remains in the plasma, and this possibility in no way invalidates our findings. Finally, we have assumed that the first pass washout curves for ICG and propranolol are identical in timing. Our own studies in dogs have revealed no difference in timing of the curves for the two substances.

These results may have important practical implications for intravenous drug treatment. The lung is acting as a larger capacitor situated upstream of the systemic circulation and so has considerable potential to affect systemic circulating levels of drugs. The simplest situation is that used in our study: a drug has been taken over a long period and then an additional dose is given intravenously. The increase in aortic blood level was four times greater than in those not previously taking the drug. Thus the same intravenous dose can produce a low therapeutic drug level in the aortic blood in one patient and a toxic level in another depending on what treatment they had previously received. Many drugs are taken up non-specifically by the lung (table 2) and so prior saturation of the lung by a different and unrelated drug might have the same effect. The high drug level in the systemic arterial blood might be sufficient to precipitate a cardiac dysrhythmia.

A more complex situation arises when a drug is being given intravenously to a patient whose lung is unsaturated. When a small fixed bolus is given

Table 2 *Drugs concentrated in the lung*

Noradrenaline	Medazepam
Diphenhydramine	Procainamide
Promazine	Propranolol
Morphine	Practolol
Pentazocine	Imipramine
Chlorphentermine	

at repeated intervals or a single dose given by slow injection the lung uptake will change with time. Initially the lung will take up most of the drug but as more binding sites become saturated a greater proportion of drug will pass through the lungs. In this way each increment of drug given will have a progressively greater effect on the systemic blood level. The relation between dose and arterial blood level will be modified so that at the low doses the curve is concave upward allowing a relatively rapid transition from minimal therapeutic to dangerous levels. This analysis is largely speculative but may help to explain some of the early anecdotal accounts of unexpected side effects of beta-blocking drugs when given in repeated doses, as well as providing further reason for giving all intravenous drugs slowly.

The method used to study lung uptake is simple and quick and furthermore may prove reliable for other studies of the pulmonary circulation in health and disease.

References

Anderson, M W, Orton, T C, Pickett, R D, and Eling, T E (1974). Accumulation of amines in the isolated perfused rabbit lung. *Journal of Pharmacology and Experimental Therapeutics*, **189**, 456–466.

Brown, E A (1974). The localisation, metabolism and effects of drugs and toxicants in the lung. *Drug Metabolism Reviews*, **3**, 33–87.

Dollery, C T, and Junod, A F (1976). Concentration of (±) propranolol in isolated, perfused lungs of rat. *British Journal of Pharmacology*, **57**, 67–71.

Evans, G H, Nies, A S, and Shand, D G (1973). The disposition of propranolol. *Journal of Pharmacology and Experimental Therapeutics*, **186**, 114–122.

Gallagher, B, Christman, D, Fowler, J, McGregor, R, Wolf, A P, Som, P, Ansari, A M, and Atkins, H (1977). Radioisotope scintigraphy for the study of dynamics of amine regulation by the human lung. *Chest*, **71**, 282–284.

Hayes, A, and Cooper, R G (1971). Studies on the absorption, distribution and excretion of propranolol in rat, dog and monkey. *Journal of Pharmacology and Experimental Therapeutics*, **176**, 302–311.

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