in five subjects (weights 59–85 kg) was 63±4·5 ng/ml. The sixth subject (weight 121 kg) had a peak concentration of 24 ng/ml and was excluded from the calculation of the mean. Norfenfluramine was detectable in the plasma of all subjects 2 h after ingestion, attaining a maximum mean plasma concentration of 16 ng/ml within 4–6 hours. A constant level was maintained for a further 24–32 hours.

The biological half-life of fenfluramine estimated graphically from the terminal part of the exponential decay curve showed wide intersubject variation with values ranging from 13·8–30·1 h (mean 20·3 h) using a one compartment system.

The apparent volume of distribution was large (635 l. for a 70 kg subject and 2000 l. for a 121 kg subject) indicating extensive uptake of the drug by the tissues and would appear to be dependent on body weight. Preliminary studies in animals, indicate that the muscle and lung contain a large proportion of the drug.

One female and five male subjects ingested one sugar-coated fenfluramine hydrochloride tablet (20 mg) at approximately 8 h intervals for 9–14 days. Blood samples were withdrawn for analysis at the same time of day for each subject at periods throughout the trial. Plasma concentrations of fenfluramine reached a plateau after 3–4 days in all subjects but varied from 40–120 ng/ml. These intersubject variations in steady state concentrations may be explained by differences in the biological half lives and volumes of distribution found between subjects.

The plateau concentrations of norfenfluramine were reached in approximately 3–4 days with plasma concentrations similar to those of the parent drug. Norfenfluramine produces weight reduction in rats and dogs (Beregi, Hugon, Le Douarec, Laubie & Duhault 1970) and therefore this compound may be an active metabolite in humans.

REFERENCES

BEREGI, L. G., HUGON, P., LE DOUAREC, J. C., LAUBIE, M. & DUHAULT, J. (1970). Structure-activity relationships in CF_3 substituted phenethylamines. In: *Amphetamines and Related Compounds*, ed. Costa, E. & Garattini, S.,'p. 29. New York: Raven Press.

CAMPBELL, D. B. (1970). A gas liquid chromatographic method for the measurement of Fenfluramine and its de-ethylated metabolite, Norfenfluramine, in plasma and urine. *J. Chromatog.*, **49**, 442–447.

Pharmacokinetics of inhaled salbutamol in asthmatic patients

MARION E. EVANS, J. W. PATERSON*, A. J. RICHARDS and S. R. WALKER
Asthma Research Council Clinical Pharmacology Unit, Institute of Diseases of the Chest, Brompton Hospital, London SW3

Salbutamol, 2-t-butylamino-1-(4-hydroxy-3-hydroxymethyl)-phenylethanol, is a non-catechol β-adrenoceptor stimulant. It is selective in man, having more effect on β_2 than on β_1 receptors (Paterson, Courtenay Evans & Prime, 1971), and has become widely used as a pressurized aerosol in the treatment of asthma.

Studies were carried out in four asthmatic patients. The drug was inhaled from a specially prepared pressurized aerosol, which delivered 0·1 mg of ^{3}H-salbutamol per dose. Venous blood samples were taken at appropriate intervals, and urine was collected for 48 hours. Changes in lung function were measured using a Vitalograph.

In two patients who received two doses the peak plasma concentrations were 2·95 and 3·57 nM, and in the two subjects who inhaled four doses the peak concentrations were 4·41 and 5·69 nM. The peak plasma concentrations were seen at 3–4 h after inhalation, and the average half life of plasma activity was 4·6 h (range 3·1–7·1 h).

Between 77·5 and 96·8% of the estimated dose was recovered in the urine in 48 hours. Urine radioactivity consisted of an unidentified metabolite (46·4–60%) and unchanged salbutamol.

Improvement in lung function occurred within 5 min of inhalation of salbutamol and did not correlate with drug plasma concentrations.

The pattern of metabolism following oral administration of salbutamol is very similar, suggesting that most of the aerosol dose was in fact swallowed as has been reported for isoprenaline (Blackwell, Conolly, Davis & Dollery, 1970; Evans, Richards, Walker & Paterson, 1971).

This work was supported by a grant from the Medical Research Council.

REFERENCES

BLACKWELL, E. W., CONOLLY, M. E., DAVIS, D. S. & DOLLERY, C. T. (1970). The fate of isoprenaline administered by pressurized aerosols. *Br. J. Pharmac.*, **39**, 194–195*P*.

EVANS, M. E., RICHARDS, A. J., WALKER, S. R. & PATERSON, J. W. (1971). The fate of [^{3}H]-salbutamol in man. *Proc. Biochem. Soc., July.*

PATERSON, J. W., COURTENAY EVANS, R. J. & PRIME, F. J. (1971). Selectivity of bronchodilator action of salbutamol in asthmatic patients. *Br. J. Dis. Chest*, **65**, 21–38.

Human pharmacology of indoramin

D. J. COLTART, J. D. F. LOCKHART, R. B. ROYDS* and P. TURNER
Department of Clinical Pharmacology, St. Bartholomew's Hospital, London EC1 and John Wyeth & Brother Limited, Taplow, Nr. Maidenhead, Berks

The effects of indoramin, a new hypotensive drug with competitive α-adrenoceptor blocking properties (Alps, Hill, Johnson & Wilson, 1970) have been studied in healthy human adult volunteers.

In a double blind investigation of six subjects indoramin (20 mg) orally produced a marked fall in blood pressure and a rise in heart rate at high exercise loads when compared with placebo. One hypertensive volunteer was studied under identical circumstances and demonstrated marked falls of resting supine and erect blood pressures as well as those after exercise. He did not suffer from symptoms referable to exercise-induced hypotension.

The effect on erect blood pressure, critical flicker frequency (CFF) (Turner, 1968), histamine skin wheal and phenylephrine-induced mydriasis was studied in a further six subjects following the double blind random administration of placebo and indoramin (20 mg and 40 mg). A dose related reduction in blood pressure and rise in heart rate was demonstrated but there was no significant effect on CFF. A dose related reduction in the size of histamine-induced skin wheals was observed (Hedges, Hill, Maclay, Newman-Taylor & Turner, 1971). There was a reduction of phenylephrine-induced mydriasis (Turner & Sneddon, 1968) followed by a dose related meiosis.

The pressor response to intravenous noradrenaline in three subjects was shifted to the right after the intravenous administration of 20 mg indoramin as shown in Fig. 1.

Indoramin (20 mg) orally twice daily for 2 weeks to four subjects reduced erect and supine blood pressures with no effect on pulse rate. Estimations of plasma concentrations of indoramin showed no evidence of accumulation. In no investigation was there any drug-related effect on liver function tests, haematology, or urea and electrolytes.

These studies in man confirm some of the pharmacological actions of indoramin found in experimental animals (Alps, Hill, Johnson & Wilson, 1970).