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.

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

REFERENCES

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

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

GRIFFIN, J. P. & TURNER, P. (1971). Preliminary studies of a new bronchodilator (WG. 253) in man. *J. clin. Pharmac.*, **11**, 280–287.

SHENFIELD, G. M. & PATERSON, J. W. (1973). Clinical assessment of bronchodilator drugs delivered by aerosol. *Thorax*, **28**, 124–128.

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

B. R. GRAHAM, D. W. LITTLEJOHNS, B. N. C. PRICHARD, B. SCALES and P. SOUTHORN*

Department of Clinical Pharmacology, Medical Unit, University College Hospital Medical School, London W.C.1, and Biochemical Pharmacology Section, I.C.I. Pharmaceutical Division, Alderley Park, Macclesfield

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.

Three subjects received placebo, 100, 200, 400 or 800 mg I.C.I. 66082 or 80 mg propranolol randomized and double blind. I.C.I. 66082 200 mg produced maximum inhibition of heart rate (H.R.) on tilting, 61±9·3 (mean±S.E. mean), placebo 79±9·3, $p<0.05$. After 3 min cycling (100 W), almost maximum inhibition was observed following 100 mg I.C.I. 66082, H.R. 85±5·8, placebo H.R. 109±5·8 ($p<0.05$); 800 mg produced little further inhibition (H.R., 83±7·1). Increased sympathetic stimulation dissociated the effect of the various dose levels, e.g., after 150 W, placebo H.R. 133±8·7, 100 mg 103±6·7 $p<0.05$; 200 mg H.R. 100±4·0, then progressively falling until after 800 mg the H.R. was 92±6·0, after propranolol 80 mg the H.R. was 99±4·8. I.C.I. 66082 diminished the rise of exercise blood pressure e.g., 150 W placebo, mean pressure 100 mmHg±5·8 following 800 mg I.C.I. 66082 86 mmHg±8·7 ($p<0.05$).

Blood levels obtained between 1·25 mg and 40 mg I.V., 100 mg and 800 mg orally, were proportional to the dose. One minute blood levels after 10 mg I.V. (0·36 μg/ml) decreased initially with a $T\frac{1}{2}$ of 20–30 min, then $T\frac{1}{2}$ increased and at 1–2 h after injection reached a maximum 5–6 h. Red cell drug concentration is 20% higher than plasma. Orally, peak levels occur at about 3 h and are calculable from the equation: peak blood levels μg/ml=oral dose (mg/kg)×0·44. Most peak levels are close to these obtained 3 h after a similar I.V. dose. Then they appear to decrease with a $T\frac{1}{2}$ of 5–6 h. Usually the drug was well absorbed (>50%, similar to most laboratory animals), occasional doses were poorly absorbed as indicated by low blood levels and low urinary excretion.

I.C.I. 66082 is therefore an effective β-adrenoceptor blocking drug in man. Experiments examining cardioselectivity are in progress. Doses of I.C.I. 66082 producing equivalent inhibition of exercise tachycardia are only one-third as active as propranolol inhibiting isoprenaline, the pattern expected from a drug showing selectivity (see Table 1). Half-life measurements indicate twice or thrice daily dosage is appropriate.

REFERENCES

BARRETT, A. M., CARTER, J., FITZGERALD, J. D., HULL, R. & LE COUNT, D. (1973). A new type of cardioselective adrenoceptive blocking drug. *Br. J. Pharmac.*, **48**, 340P.

HAINSWORTH, R., KARIM, F. & STOKER, J. B. (1973). The blocking effects of propranolol, practolol and ICI-66082 on the peripheral vascular responses to isoprenaline. *Br. J. Pharmac.*, **48**, 342P.

HARRY, J. D., KNAPP, M. F., & LINDEN, R. J. (1973). The action of ICI-66082 on the heart. *Br. J. Pharmac.*, **48**, 340P.

The influence of urine pH on the renal excretion of practolol and propranolol

C. M. KAYE*, D. G. ROBINSON and P. TURNER

Department of Clinical Pharmacology, St. Bartholomew's Hospital, London EC1A 7BE

The absorption of four β-adrenoreceptor blocking drugs through the buccal mucous membrane has been studied by Hicks (1973) over a pH range of 5·5–9·5. The absorption of propranolol and Ro 3–3528 (6–7—dimethyl–α–isopropylamino-methyl–2–benzofuranmethanol) was pH dependent, while that of practolol and pindolol appeared to be almost independent of pH. It is known that practolol and propranolol have similar pKa values, 9·5 and 9·45 respectively, but different partition coefficients, 0·19 and 28·5 respectively. The possibility that reabsorption of these two drugs across the renal tubular epithelium is similarly pH dependent has been investigated.

Four normal, male volunteers each took propranolol (80 mg) or practolol (200 mg) on three separate occasions so that the excretion of each drug could be determined with the urine pH uncontrolled, or acidified by ammonium chloride ingestion, or alkalinized by sodium bicarbonate ingestion (Beckett & Rowland, 1965). The 24 h excretion of propanolol was measured fluorimetrically (Shand, Nuckolls & Oates, 1970), and practolol spectrophotometrically (Turner, Burnam, Hicks, Cherrington, MacKinnon, Waller & Woolnough, 1971).

The results are given in Table 1. The urinary excretion of propranolol markedly decreased in all four subjects as the pH of the urine rose, whereas with practolol the urine