found a significant impairment of performance in a pursuit-rotor test after oxprenolol 0.2 mg/kg intravenously.

Although it would appear that any changes which occur in central nervous function after the usual oral doses (10-80 mg) of propranolol are small, it is possible that more marked changes might occur with the larger doses sometimes used in hypertension and angina pectoris. It is uncertain to what extent, if any, the small changes demonstrated in this study are important in mediating the therapeutic actions of propranolol in anxiety states.

We thank Imperial Chemical Industries Ltd and in particular Dr P.F.C. Bayliss, for supplying the tablets used in this study and for carrying out the statistical analysis.

P.C. BRYAN, D.O. EFIONG &
J. STEWART-JONES

Department of Ophthalmic Optics & Visual Science, The City University, London, EC1V 9HH

P. TURNER

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

Received August 28, 1973

References

- AUSTEN, D.P. GILMARTIN, B.A. & TURNER, P. (1971). The effect of chlordiazepoxide on visual field, extraocular muscle balance, colour matching ability and hand-eye co-ordination in man. *Br. J. Physiol. Opt.*, **26**, 161-165.
- BELL, R.W., DICKIE, D.S., STEWART-JONES, J. & TURNER, P. (1973). Lorazepam on visuo-motor co-ordination and visual function in man. *J. Pharm. Pharmacol.*, **25**, 87.
- BONN, J.A. & TURNER, P. (1971). D-propranolol and anxiety. *Lancet*, **i**, 1355-1356.
- BONN, J.A., TURNER, P. & HICKS, D. (1972). β -adrenergic receptor blockade with practolol in treatment of anxiety. *Lancet*, **i**, 814-815.
- GLAISTER, D.H., HARRISON, M.H. & ALLNUTT, M.F. (1973). Experimental cardiovascular stress and the influence of oxprenolol. In: *New Perspectives in β -blockade*. ed. Burley, D.M., Frier, J.H., Rondel, R.K. & Taylor, S.H. Ciba, Horsham, England.
- GRANVILLE-GROSSMAN, K.L. & TURNER, P. (1966). The effect of propranolol on anxiety. *Lancet*, **i**, 778-790.
- LADER, M.H. & TYRER, P.J. (1972). Central and peripheral effects of propranolol and sotalol in normal human subjects. *Br. J. Pharmacol.*, **45**, 557-560.
- MOLSON, G.R., MACKAY, J.A., SMART, J.V. & TURNER, P. (1966). Effect of promethazine hydrochloride on hand-eye co-ordination. *Nature, Lond.*, **209**, 516.
- TURNER, P. & HEDGES, A. (1973). An investigation of the central effects of oxprenolol. In: *New Perspectives in β -blockade*. ed. Burley, D.M., Frier, J.H., Rondel, R.K. & Taylor, S.H. Ciba, Horsham, England.

A SIMPLE SPECTROPHOTOFUOROMETRIC METHOD FOR THE MEASUREMENT OF I.C.I. 66082 IN PLASMA AND URINE

Preliminary studies in animals with I.C.I. 66082, 4-(2-hydroxy-3-isopropylaminopropoxy) phenyl acetamide, indicated that it was a cardioselective β -adrenoreceptor blocking agent without intrinsic sympathomimetic or membrane activity (Barrett, Carter, Fitzgerald, Hull & Le Count, 1973; Harry, Knapp & Linden, 1973; Hainsworth, Karim & Stoker, 1973), and initial observations on its human pharmacology have shown that it is an effective β -adrenoceptor blocking drug in man (Graham, Littlejohns, Prichard, Scales & Southorn, 1973). The present work describes a simple spectrophotofluorometric method for the measurement of I.C.I. 66082 in plasma and urine, and gives the results obtained by this method for levels of the drug in plasma and urine of two normal male volunteers who received 200 mg of I.C.I. 66082 orally in a tablet formulation.

The excitation and emission spectra of I.C.I. 66082 are shown in Figure 1. With the emission wavelength set at 310 nm curve A was obtained by scanning the excitation spectrum of the pure drug in 0.5 M aqueous NaH_2PO_4 solution at a concentration of 5 $\mu\text{g/ml}$. On scanning the emission spectrum of the same sample with the excitation wavelength set at 280 nm, curve B was obtained. Three peaks occurred in the excitation spectrum, the main one being at 280 nm, and two peaks occurred in the emission spectrum, the main one being at 310 nm. In the present method for measuring I.C.I. 66082 the excitation wavelength was set at 280 nm and the emission wavelength at 310 nm.

The method used for plasma was as follows. To plasma (2 ml) was added 10 M NaOH (0.2 ml) and ethyl acetate (12 ml). The mixture was shaken

Fig. 1 Excitation (A) and emission (B) spectra of I.C.I. 66082 (5 $\mu\text{g/ml}$ in 0.5 M aqueous NaH_2PO_4 solution).

mechanically for 15 min and then centrifuged for 5 minutes. The upper ethyl acetate layer (10 ml) was added to 0.5 M aqueous NaH_2PO_4 solution (2 ml) and the drug was back extracted into the phosphate solution by shaking for 10 minutes. After centrifuging for 5 min the fluorescence of the lower aqueous phase was measured in an Aminco-Bowman spectrophotofluorometer with excitation wavelength 280 nm and emission wavelength 310 nm. A standard curve was obtained by adding known amounts of the drug to blank plasma and subjecting these samples to the above procedure. The curve was found to be linear up to a concentration of at least 20 $\mu\text{g/ml}$ of I.C.I. 66082 in plasma.

The method for urine was the same as described above for plasma except that 1 ml of urine was used and 0.1 ml of 10 M NaOH was added to it. The standard curve of I.C.I. 66082 in urine was linear up to a concentration of 100 $\mu\text{g/ml}$, and urine samples more concentrated than this were suitably diluted. The limit of detection of the method was of the order of 0.05 $\mu\text{g/ml}$, and it must be considered a possibility that metabolites of I.C.I. 66082, if they exist, may contribute to the total fluorescence measured.

Two normal healthy volunteers (S_1 and S_2) both aged 28 years each received an oral dose of 200 mg of I.C.I. 66082 and blood samples were withdrawn at 0, 1, 2, 3, 4, 6, 8 and 24 hours. The plasma levels of the drug were measured by the above procedure and the results are shown in Table 1. The two subjects differed markedly in the time at which peak plasma level of the drug was attained, S_1 having a peak level of 1.09 $\mu\text{g/ml}$ at 2 h and S_2 a peak level of 0.96 $\mu\text{g/ml}$ at 6 hours.

Table 1 Levels of I.C.I. 66082 in the plasma and urine of two normal male volunteers (S_1 and S_2) following a 200 mg oral dose

Time (h)	Plasma level ($\mu\text{g/ml}$)	
	S_1	S_2
0	0.00	0.00
1	0.16	ND
2	1.09	0.15
3	0.93	0.61
4	0.71	0.91
6	0.60	0.96
8	0.47	0.76
24	0.05	0.19

	Urine content (mg)	
	S_1	S_2
0	0.0	0.0
0-2	10.2	0.8
2-4	16.5	18.2
4-6	14.5	20.5
6-8	10.0	13.0
8-24	26.9	34.3
Total 0-24	78.1	86.8

ND = Not detected, i.e. <0.05 $\mu\text{g/ml}$.

Also, the plasma elimination half-life of the drug differed between the two subjects, S_1 having a $T_{1/2}$ of 5.0 h and S_2 a $T_{1/2}$ of 7.8 hours.

Urine samples were collected from the two subjects at 0, 0-2 h, 2-4 h, 4-6 h, 6-8 h and 8-24 h, and the results obtained by the above method are shown in Table 1. As with the plasma samples these results suggest that S_1 absorbed the drug faster than S_2 since significant amounts of the drug appeared in the urine of S_1 earlier than in the urine of S_2 . The total amount of I.C.I. 66082 excreted in the urine of S_1 and S_2 in 24 h was similar, being 78.1 mg and 86.8 mg respectively. Further investigations will be required to ascertain whether the excretion of about 40% of the dose in the urine in 24 h reflects the incomplete absorption of I.C.I. 66082 and/or its substantial metabolism in man.

I thank the British Heart Foundation for financial support, and I.C.I. Ltd for supplying I.C.I. 66082.

C.M. KAYE

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

Received August 29, 1973

References

- BARRETT, A.M., CARTER, J., FITZGERALD, J.D., HULL, R. & LE COUNT, D. (1973). A new type of cardioselective adrenoreceptive blocking drug. *Br. J. Pharmac.*, **48**, 340P.
- GRAHAM, B.R., LITTLEJOHNS, D.W., PRICHARD, B.N.C., SCALES, B. & SOUTHOORN, P. (1973). Preliminary observations on the human pharmacology of I.C.I. 66082 in normal volunteers. *Br. J. Pharmac.*, **49**, 154P.
- HAINSWORTH, R., KARIM, F. & STOKER, J.B. (1973). The blocking effects of propranolol, practolol and I.C.I. 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 I.C.I. 66082 on the heart. *Br. J. Pharmac.*, **48**, 340P.

THE RENAL EXCRETION OF MEXILETINE (Kö 1173) UNDER CONTROLLED CONDITIONS OF URINE pH

Recent studies of mexiletine, Kö 1173 (1-[2,6-dimethylphenoxy] 2-aminopropane), a primary amine, have shown it to be a useful drug in the treatment of ventricular dysrhythmias (Talbot, Clark, Nimmo, Neilson, Julian & Prescott, 1973; Campbell, Chaturvedi, Kelly, Strong, Shanks & Pantridge, 1973). Beckett & Rowland (1964) demonstrated that the urinary excretion of amphetamine, a primary amine of similar structure to mexiletine, was markedly pH dependent, and so the influence of pH on the urinary excretion of mexiletine has been investigated.

Four normal healthy volunteers received 2 x 100 mg capsules of mexiletine orally on three separate occasions, when their urine pH was either uncontrolled, acidified by ammonium chloride ingestion or alkalinized by sodium bicarbonate ingestion (Beckett & Rowland, 1965). Urine was collected 2 hourly up to 8 h and then from 8-24 hours.

The amount of parent drug in each sample (Fig. 1) was determined by the GLC method described by Kiddie, Royds & Shaw (1973), which is similar to that recently reported by Kelly, Nimmo, Rae, Shanks & Prescott (1973); the pH of each urine sample was adjusted to 11.9 by the addition of 1.5 ml Sørensen glycine buffer. A number of standard curves were obtained by adding known amounts of mexiletine to normal pooled urine and were found to be linear over the range 0-250 µg/ml using suitable concentrations of internal standard.

From Fig. 1 it can be seen that the urinary excretion of mexiletine is markedly pH dependent. Under normal conditions, urine pH ranged from 5.40-7.00 and this resulted in the amount of unchanged mexiletine excreted in 24 h being variable, ranging from 5.9% of the dose in Subject 1 (mean pH 6.41 in 24 h) to 10.1% in Subject 3 (mean pH 5.79 in 24 hours). This subject, however, with a mean pH in acidic conditions of 4.88

Fig. 1 The influence of urine pH on the renal excretion of mexiletine (Kö 1173) in 24 hours. Acid pH—cross-hatched columns; uncontrolled pH—single-hatched columns; alkaline pH—solid columns.

excreted 50.2% of the dose but only 0.4% when the mean urine pH was 8.0.

Further investigation is in process to determine whether variation in urinary pH may affect the pharmacokinetics of mexiletine.

We thank the British Heart Foundation and Boehringer Ingelheim Ltd for financial support. Mexiletine was provided by Boehringer Ingelheim Ltd.

MOIRA A. KIDDIE & C.M. KAYE

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

Received September 26, 1973