Br. J. Pharmac. (1973), **49**, 106–114.

Assessment of selective β-adrenoceptor blockade in man

R. H. BRIANT, C. T. DOLLERY, T. FENYVESI* AND C. F. GEORGE

M.R.C. Clinical Pharmacology Research Group, Royal Postgraduate Medical School, London W.12

Summary

1. Selective antagonism of the cardiac β_1-adrenoceptors has been studied in normal human volunteers.

2. Practolol and UK 6558 produced greater antagonism of the chronotropic and inotropic responses to i.v. isoprenaline than of the vasodilator response to either i.v. or intra-arterial isoprenaline. A third drug, M&B 17,803A, produced non-selective β-adrenoceptor blockade in 2 of 3 subjects studied.

3. Practolol, UK 6558 and M&B 17,803A, produced an attenuation of the responses to Valsalva's manoeuvre.

4. A substantial reduction in blood pressure was seen in 3 of 4 normotensive subjects given UK 6558.

Introduction

β-adrenoceptor antagonists are widely used in the treatment of angina pectoris, arterial hypertension and cardiac arrhythmias. Among the important complications of this form of treatment is the development of bronchospasm (Stephen, 1966; Zacharias, 1971), especially in patients with pre-existing obstructive airways disease. As many patients with angina or hypertension also have airways disease, this may prevent the use of conventional β-adrenoceptor antagonists. The observations of Levy (1964; 1966) and Lands & Brown (1964) that the β-adrenoceptors in the heart differ from those elsewhere in the body led to the development of practolol, a drug which in animals has been shown to produce selective blockade of the cardiac β-adrenoceptors (Barrett, Crowther, Dunlop, Shanks & Smith, 1968; Dunlop & Shanks, 1968). Although practolol has been shown to be effective in the treatment of angina pectoris (Areskog & Adolfsson, 1969; George, Nagle & Pentecost, 1970), cardiac arrhythmias (Jewitt, Mercer & Shillingford, 1969; Gent, Davis & McDonald, 1970; Allen, Pantridge & Shanks, 1971) and hypertension (Prichard, Boakes & Day, 1971) attempts to evaluate the selective action of this compound in man have been less successful (Barrett, 1971). This paper describes an attempt to evaluate selective blockade of the β_1-adrenoceptors in man by practolol and two other compounds, M&B 17,803A (May & Baker) and UK 6558 (Pfizer) (Figure 1). The methodology used represents a modification of the techniques employed by Brick, Hutchison, McDevitt, Roddie & Shanks (1968).

Methods

The studies were performed in nine normal volunteers aged 23–45 who gave their consent after a full explanation of the procedure (Table 1). A polyethylene catheter

* Present address: Semmelweis University Medical School, Ulloi-ut 26, Budapest, Hungary.

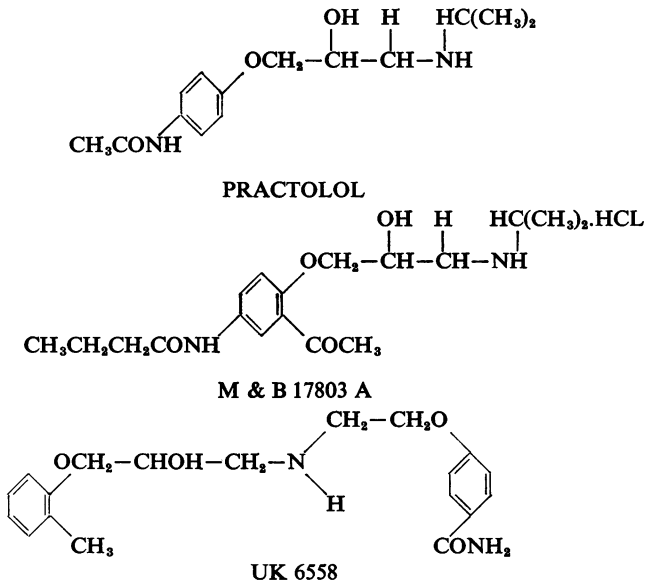


FIG. 1. Structural formulae of the 3 β-adrenoceptor antagonists studied.

TABLE 1. *Details relating to the subjects studied*

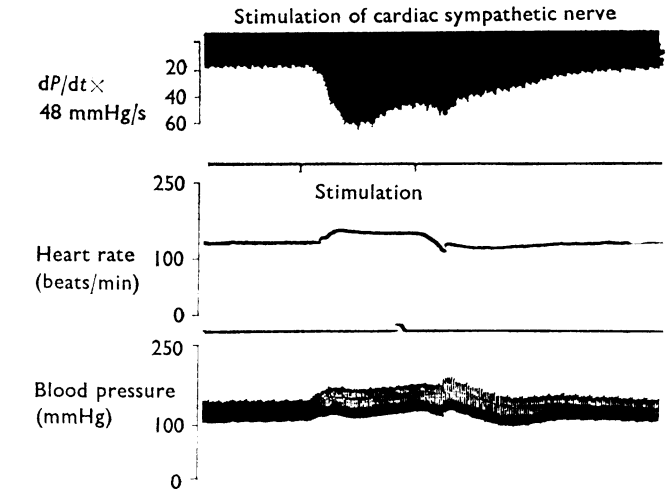
Subject No.	Age	Sex	Wt. (kg)	Drug given	Route
1	43	F	46·0	Practolol	i.v.
2	30	M	57·2	Practolol	p.o.
3	45	M	82·9	UK 6558	i.v.
4	42	M	80·9	UK 6558	p.o.
5	24	M	77·7	UK 6558	i.v.
6	39	M	86·6	UK 6 58	p.o.
7	28	M	87·2	M&B517,803A	p.o.
8	23	M	69·0	M&B 17,803A	p.o.
9	31	M	81·0	M&B 17,803A	i.v.

(P.E. 60) was introduced up one brachial artery under local anaesthesia using the Seldinger technique. Through this line arterial blood pressure was monitored with a transducer (Bell & Howell) and, by differentiating the signal electrically, axillary artery dP/dt was derived and was used as a measure of cardiac contractility. The evidence that this parameter gives a measure of cardiac contractility is derived from observations in normal man, Parkinsonian patients (Reid, Calne, George, Pallis & Vakil, 1971 ; Reid, Calne, George & Vakil, 1972) and anaesthetized dog and is as follows:

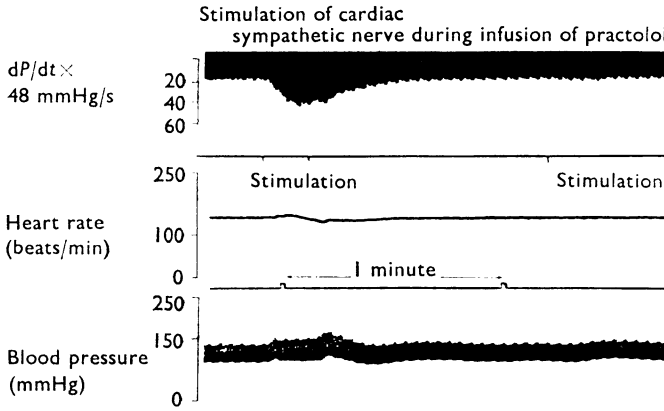
(a) The increase in dP/dt after i.v. isoprenaline and stellate ganglion stimulation is specifically and reversibly antagonized by β-adrenoceptor blockade (Figure 2).

(b) The increase in dP/dt seen after stimuli such as i.v. isoprenaline is not solely a reflection of changes in heart rate as a considerable increase in dP/dt is seen during the overshoot in blood pressure following Valsalva's manoeuvre simultaneous with cardiac slowing.

(c) Changes in peripheral resistance make little or no difference to the response. This holds true for the pressor response to infused noradrenaline, as well as for reactive hyperaemia. Where selective β-adrenoceptor blockade was demonstrated the dose-ratio−1 for dP/dt was similar to that seen for heart rate and greater than the antagonism of either the diastolic pressure or the forearm blood flow responses to isoprenaline.



(a)



(b)

FIG. 2. (a) Effect of stimulating the cardiac sympathetic nerve on heart rate, blood pressure and axillary artery dP/dt in anaesthetized dog. (b) Stimulation of cardiac sympathetic nerve during infusion of practolol 2 mg/min i.v.

Three minute infusions of isoprenaline sulphate were given through the arterial line and increases in forearm blood flow were measured by venous occlusion plethysmography (Greenfield, Whitney & Mowbray, 1963).

Intravenous injections of isoprenaline were given through a butterfly needle inserted in a forearm vein of the opposite arm (George, Conolly, Fenyvesi, Briant & Dollery, 1972). Heart rate was recorded from a continuous E.C.G. using a digital rate meter (Emons & Conolly, 1971). Because measurements of forearm blood flow interfered with those of heart rate, the forearm flow estimations were bracketed between two sets of responses to intravenous isoprenaline after β-blockade. This allowed assessment of changes in the degree of β-adrenoceptor blockade in the time lag between the two sorts of measurements.

Practolol was given once orally and once i.v., UK 6558 on two occasions orally and twice i.v., M&B 17,803A was given orally in two instances and once i.v. (Table 2).

Statistical analysis

A regression of response on log-isoprenaline dose was calculated by the method of least squares for each of the four parameters before and after β-blockade. In several instances the slopes of the pre- and post-treatment dose-response curves differed and would have resulted in variation of the dose-ratios obtained (depending upon which value of y was chosen for the calculation). However, an analysis of covariance (Snedecor & Cochran, 1967) performed on the slopes of each group of dose-response lines showed that there were no statistically significant differences in the slopes of each group of pre- and post-β-blockade dose-response curves. It was therefore assumed that the slopes were parallel and a common slope was calculated for each set of curves. The dose-ratios for each set of curves were then computed from the common slope and used to estimate the degree of β-adrenoceptor blockade. Selectivity was assessed in two ways:

(a) By dividing the dose-ratio−1 for heart rate (at maximal blockade) by that for diastolic pressure measured at the same time.

(b) Assuming that changes in the degree of blockade in terms of dose-ratio−1 of heart rate responses were exponential with time (log DR−1 varies linearly with t), an estimate of the dose-ratio for heart rate was calculated for the time of the forearm flow measurement. The ratio of the dose-ratio−1 heart rate (estimated): dose-ratio−1 forearm flow was then calculated.

If β-adrenoceptor blockade were non-selective each of these final ratios should be 1. By performing a logarithmic transformation of the data it was then possible to test the ratios obtained against zero (log 1) by Student's t test.

TABLE 2. *Degree of β-adrenoceptor blockade in relation to time after dosing*

Subject	Dose and route	Time (min)	Dose-Ratio −1 Heart rate	dP/dt	Diastolic pressure	Forearm flow
1	20 mg i.v. Practolol	38	2·7	2·7	0·4	
		83				0·4
		106	1·3	1·7	0·4	
2	300 mg oral Practolol	137	10·4	14·4	3·8	
		186				1·2
		214	7·4	9·6	6·4	
3	20 mg i.v. UK 6558	30	14·7	12·8	2·0	
		75				3·0
		105	10·6	7·2	0·8	
4	200 mg oral UK 6558	141	26·7	33·7	8·6	
		182				7·4
		222	11·0	13·9	3·5	
5	20 mg i.v. UK 6558	30	10·8	9·3	4·4	
		75				3·1
		90	6·2	2·6	4·5	
6	200 mg oral UK 6558	132	24·8	84·8	14·0	
		176				8·4
		201	13·0	34·2	11·7	
7	300 mg oral M&B 17,803A	100	13·0	40·3	12·9	
		165				29·6
		189	88·5	102·8	36·5	
8	300 mg oral M&B 17,803A	135	17·0	15·4	14·9	
		192				15·7
		212	15·4	10·1	12·4	
9	20 mg i.v. M&B 17,803A	46	4·8	6·7	4·0	
		73				17·2
		109	2·3	1·9	2·1	

TABLE 3. *Indices of selective β-adrenoceptor blockade*

Subject	$\frac{\text{H.R. dose-ratio}-1}{\text{DBP dose-ratio}-1}$ (A)	$\frac{\text{H.R. dose-ratio}-1}{\text{Flow dose-ratio}-1}$ (B)	log (A)	log (B)	*t* value and significance (A)	(B)
1	2·7/0·4	1·7/0·4	0·83	0·63		
2	10·4/3·8	8·4/1·2	0·44	0·85		
3	14·7/2·0	13·0/3·0	0·86	0·64		
4	26·7/8·6	17·4/7·4	0·49	0·37	3·82 < 0·05	5·53 < 0·02
5	10·8/4·4	7·5/3·1	0·39	0·38		
6	24·8/14·0	16·5/8·4	0·25	0·29		
7	88·5/36·5	56·0/28·4	0·38	0·29		
8	17·0/14·9	16·0/15·7	0·06	0·01	1·68 N.S.	0·45 N.S.
9	4·8/4·0	3·5/17·2	0·08	T·31		

Results

The results for all nine subjects are summarized in Tables 2 and 3.

Practolol produced greater blockade of the cardiac response than of the vasodilator responses to isoprenaline (Figure 3).

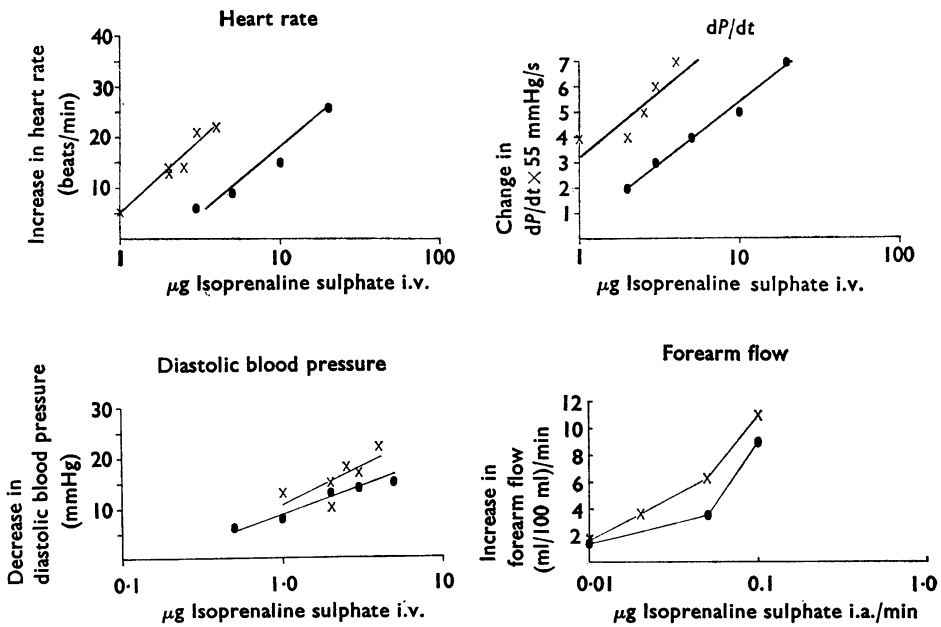


FIG. 3. Isoprenaline log dose-response curves before (×——×) and after (●——●) β-adrenoceptor blockade with practolol 20 mg i.v. (Subject 1).

UK 6558 produced significantly greater blockade of the chronotropic responses than of the forearm flow and diastolic blood pressure responses to isoprenaline $t=5{\cdot}53$, $P<0{\cdot}02$ and $t=3{\cdot}82$, $P<0{\cdot}05$ respectively (Figure 4).

M&B 17,803A failed to produce cardioselective β-adrenoceptor antagonism in two of the subjects studied (Figure 5). In the third, the vasodilator responses to isoprenaline were blocked to a lesser extent than the cardiac responses.

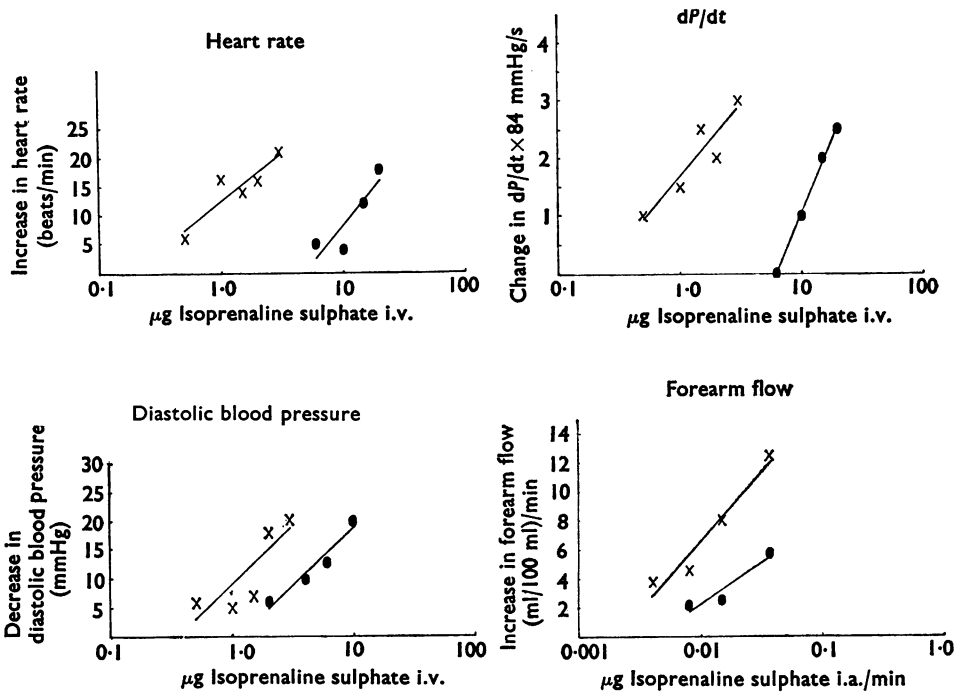


FIG. 4. Isoprenaline log dose-response curves before (×——×) and after (●——●) β-adrenoceptor blockade with UK 6558 20 mg i.v. (Subject 3).

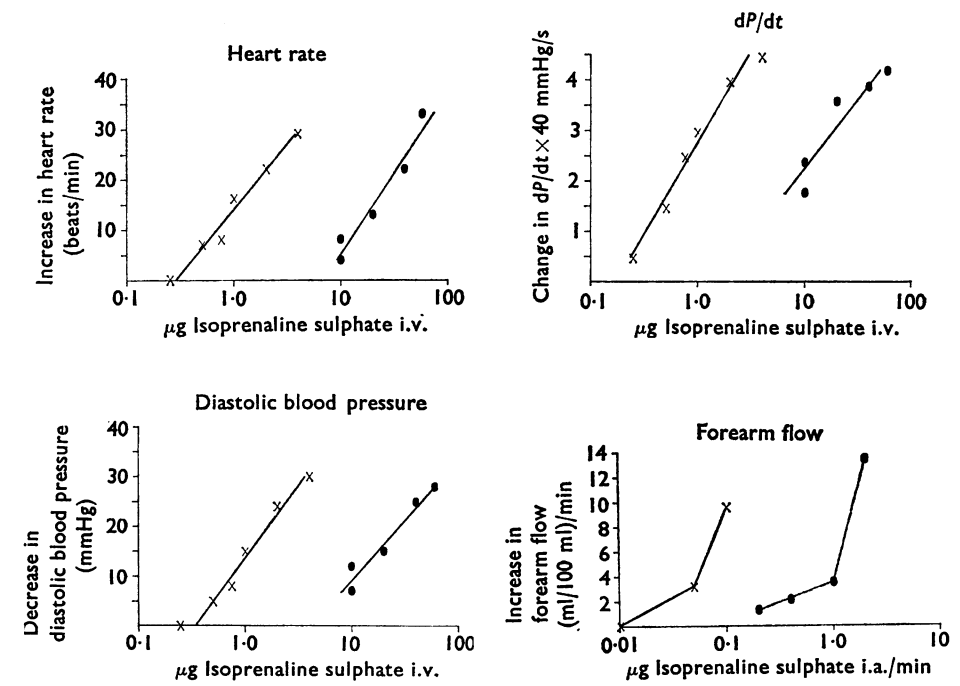


FIG. 5. Isoprenaline log dose-response curves before (×——×) and after (●——●) β-adrenoceptor blockade with M&B 17,803A 300 mg orally (Subject 8).

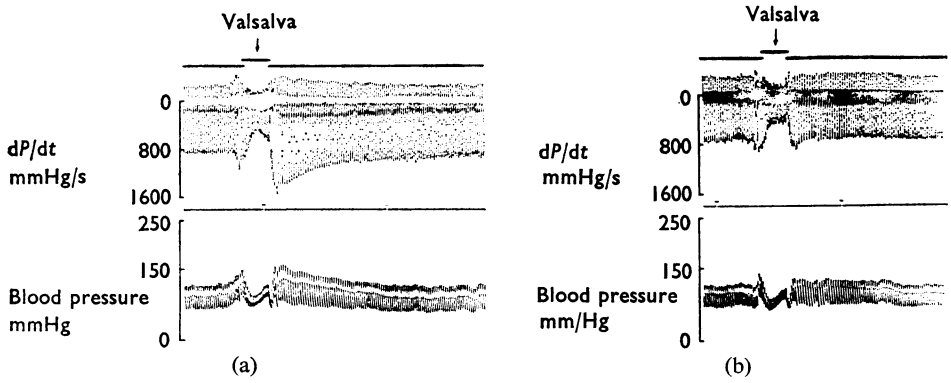


FIG. 6. (a) Intra-arterial blood pressure and axillary artery dP/dt during Valsalva's manoeuvre. (b) After β-adrenoceptor blockade.

All three compounds produced attenuation of the responses to Valsalva's manoeuvre, an example of which is shown in Figure 6. Despite a reduction in resting heart rate after both practolol and M&B 17,803A, no significant change in blood pressure was seen. In contrast, UK 6558 caused a more pronounced slowing of heart rate and a substantial reduction in blood pressure (Table 4).

TABLE 4. *Effects of β-adrenoceptor antagonists on heart rate and blood pressure*

		Basal		At time of maximum β-blockade	
Subject No.		Average B.P.	Average heart rate	Average B.P.	Average heart rate
1	Practolol	145/82	76	145/83·5	66
2		114/70	56	123/75·5	60
3		129/74	72	114/65	64
4	UK 6558	116/68·5	56	117/67	52
5		133/70·5	60	125·5/52·5	54·5
6		121/82	63	99/63	54·5
7		136/87	64	143/103	60
8	17,803A	113·5/72	55	126/73	50
9		111/63	51	107·5/62·5	48·5

	Average changes ±S.E. and t value	
	Heart rate	Blood pressure
Practolol	−3·0±7·0	4·50±4·50/3·50±2·00
	N.S.	N.S. N.S.
UK 6558	−6·50±1·06	−10·88±4·94/−11·88±4·13
	$t=6·13, P<0·01$	N.S. N.S.
M&B 17,803A	−3·83±0·73	5·67±4·95/5·50±5·27
	$t=5·27, P<0·05$	N.S. N.S.

Discussion

These investigations demonstrate that practolol and UK 6558 have a significantly greater effect on cardiac responses than on the vasodilator responses to isoprenaline. Several previous attempts have been made to demonstrate cardioselective β-adrenoceptor antagonism in man, but have met with varying degrees of success. In the study by Brick *et al.* (1968) isoprenaline was given by i.v. infusion at a single dose level. The present methodology has significant advantages, in that a limited dose-response curve gives a high degree of accuracy and repeatability (George *et al.*, 1972) and rapid i.v. injections of isoprenaline do not produce resistance (Conolly, Davies, Dollery & George, 1971). Furthermore, it is likely that the tachycardia

produced by rapid injections is mainly the result of β-adrenoceptor stimulation (Cleaveland, Rangno & Shand, 1972) whereas infusions of 3 or more min also result in a substantial reduction in vagal tone. This would explain why our technique resulted in rougly parallel shifts to the right of the dose-response curves whereas workers using the infusion technique have reported more shallow slopes of post practolol dose-response curves. Furthermore, where individual results seemed to show deviations from parallelism the averaged curves showed no systematic deviations so that dose ratios could be calculated.

Two other techniques have been used to assess cardioselective β-adrenoceptor blockade in man; in the first the chronotropic effects of inhaled isoprenaline were compared with its bronchodilating property (Powles, Shinebourne & Hamer, 1969; Palmer, Legge, Hamilton & Diament, 1969). In the second, the chronotropic effects of inhaled isoprenaline were contrasted with its ability to cause a rise in mean skin temperature over the cheek (Harrison & Turner, 1969). Both of these techniques give a qualitative guide to selective β-adrenoceptor antagonism and the latter has the advantage of being non-invasive. However, no true quantitative measure can be derived as only 1–2% of an inhaled dose actually exerts a pharmacological effect (Paterson, Conolly, Davies & Dollery, 1968) and, even in persons accustomed to using such inhalers, there is some variation in the amount inhaled.

The degree of selectivity demonstrated in the present studies was apparently greater after i.v. than after oral dosing. Two explanations are possible; the first is that in the oral studies the dose used was larger and was usually associated with a greater degree of β-adrenoceptor blockade. The latter would lead to complex haemodynamic alterations to maintain homeostasis which might reduce the diastolic pressure lowering effects of isoprenaline. Alternatively, in the oral studies, post blockade measurements were not made until 2 h or more after the dose compared with half an hour or so after i.v. dosing. It is possible that the higher degree of cardioselective β-adrenoceptor blockade seen after the i.v. dose is due to early distribution of drug to the heart but that later further uptake into vascular smooth muscle occurs.

The reduction in arterial blood pressure seen in 3 of the 4 normotensive subjects given UK 6558 is particularly interesting. Arterial blood pressure does not usually fall after i.v. propranolol despite a reduction in cardiac output (Ulrych, Frohlich, Dustan & Page, 1968), and no change in B.P. was seen in the present study after either practolol or M&B 17,803 A. However, chronic oral administration of propranolol leads to a reduction in both cardiac output and blood pressure (Frohlich, Tarazi, Dustan & Page, 1968). The explanation for these findings is uncertain; they could reflect differences in either the pharmacology of the β-adrenoceptor antagonists studied, or possibly in their metabolism.

We wish to thank Miss S. Jackson, SRN, and Miss D. F. Milne, SRN, for skilled technical assistance, and Miss A. Petrie, MSc ,for advice on the statistical analysis. We are indebted to Dr. D. R. Maxwell of May & Baker for supplies of M&B 17,803A and to Dr. E. A. Stevens of Pfizer Ltd. for the UK 6558 and financial support. The practolol was given by ICI Ltd. who also provided financial assistance. R. H. B. is in receipt of a Wellcome Scholarship in Clinical Pharmacology.

REFERENCES

ALLEN, J. D., PANTRIDGE, J. F. & SHANKS, R. G. (1971). Practolol in the treatment of ventricular dysrhythmias in acute myocardial infarction. *Postgrad. med. J.*, **47**, Suppl. 29–35.

ARESKOG, N-H & ADOLFFSON, L. (1969). Effects of a cardioselective β-adrenergic blocker (ICI 50,172) at exercise in angina pectoris. *Brit. med. J.*, **2**, 601–603.

BARRETT, A. M., CROWTHER, A. F., DUNLOP, D., SHANKS, R. G. & SMITH, L. H. (1968). Cardioselective β-blockade. *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.*, **259**, 152–153.

BARRETT, A. M. (1971). The pharmacology of practolol. *Postgrad. med. J.*, **47**, Suppl. 7–12.

BRICK, I., HUTCHISON, K. F., MCDEVITT, D. G., RODDIE, I. C. & SHANKS, R. G. (1968). Comparison of the effects of ICI 50,172 and propranolol on the cardiovascular responses to adrenaline, isoprenaline and exercise. *Br. J. Pharmac. Chemother.*, **34**, 127–140.

CLEAVELAND, C. R., RANGNO, R. E. & SHAND, D. G. (1972). A standardized isoproterenol sensitivity test. *Arch. int. Med.* **130**, 47–52.

CONOLLY, M. E., DAVIES, D. S., DOLLERY, C. T. & GEORGE, C. F. (1971). Resistance to β-adrenoceptor stimulants (a possible explanation for the rise in asthma deaths). *Br. J. Pharmac.*, **43**, 389–402.

DUNLOP, D. & SHANKS, R. G. (1968). Selective blockade of adrenoceptive β-receptors in the heart. *Br. J. Pharmac. Chemother*, **32**, 201–218.

EMONS, E. & CONOLLY, M. E. (1971). Digital heart ratemeter. *Cardiovasc. Res.*, **5**, 157–160.

FROHLICH, E. D., TARAZI, R. C., DUSTAN, H. P. & PAGE, I. M. (1968). The paradox of beta-adrenergic blockade in hypertension. *Circulation*, **37**, 417–423.

GENT, G., DAVIS, T. C. & MCDONALD, A. (1970). Practolol in treatment of supraventricular cardiac dysrhythmias. *Brit. med. J.*, **1**, 533–535.

GEORGE, C. F., CONOLLY, M. E., FENYVESI, T., BRIANT, R. H. & DOLLERY, C. T. (1972). Isoproterenol sulfate dose-response curves in man. *Arch. Intern. Med.*, **130**, 361–364.

GEORGE, C. F., NAGLE, R. E. & PENTECOST, B. L. (1970). Practolol in treatment of angina pectoris. A double blind trial. *Brit. med. J.*, **2**, 402–404.

GREENFIELD, A. D. M., WHITNEY, R. J. & MOWBRAY, J. F. (1963). Methods for the investigation of peripheral blood flow. *Brit. med. Bull.*, **19**, 101–109.

HARRISON, J. & TURNER, P. (1969). Comparison of propranolol and ICI 50,172 on isoprenaline-induced increase in skin temperature in man. *Br. J. Pharmac.*, **36**, 177P.

JEWITT, D. E., MERCER, C. J. & SHILLINGFORD, J. P. (1969). Practolol in the treatment of cardiac dysrhythmias due to acute myocardial infarction. *Lancet*, **ii**, 227–230.

LANDS, A. M. & BROWN, T. D. (1964). A comparison of the cardiac stimulating and bronchodilator actions of selected sympathomimetic amines. *Proc. Soc. exp. Biol.*, **116**, 331–333.

LEVY, B. (1964). Alterations of adrenergic responses by N-isopropylmethoxamine. *J. Pharmac. exp. Ther.*, **146**, 129–138.

LEVY, B. (1966). Dimethyl isopropylmethoxamine: a selective beta receptor blocking agent. *Br. J. Pharmac. Chemother.*, **27**, 277–285.

PALMER, K. N. V., LEGGE, J. S., HAMILTON, W. F. D. & DIAMENT, M. L. (1969). Effect of a selective β-adrenergic blocker in preventing falls in arterial oxygen tension following isoprenaline in asthmatic subjects. *Lancet*, **ii**, 1092–1094.

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

POWLES, R., SHINEBOURNE, E. & HAMER, J. (1969). Selective cardiac sympathetic blockade as an adjunct to bronchodilator therapy. *Thorax*, **24**, 616–618.

PRICHARD, B. N. C., BOAKES, A. J. & DAY, G. (1971). Practolol in the treatment of hypertension. *Postgrad. med. J.*, **47**, Suppl. 84–91.

REID, J. L., CALNE, D. B., GEORGE, C. F., PALLIS, C. & VAKIL, S. D. (1971). Cardiovascular reflexes in Parkinsonism. *Clin. Sci.*, **41**, 63–67.

REID J. L. CALNE, D. B., GEORGE, C. F. & VAKIL, S. D. (1972). Levodopa and pressor amine sensitivity in Parkinsonism. *Clin. Pharmacol. Therap.*, **13**, 400–406.

SNEDECOR, G. W. & COCHRAN, W. G. (1967). In *Statistical Methods*, 14–16. Ames, Iowa, Iowa State University Press.

STEPHEN, S. A. (1966). Unwanted effects of propranolol. *Amer. J. Cardiol.*, **18**, 463–468.

ULRYCH, M., FROHLICH, E. D., DUSTAN, H. P. & PAGE, I. H. (1968). Immediate hemodynamic effects of beta-adrenergic blockade with propranolol in normotensive and hypertensive men. *Circulation*, **37**, 411–416.

ZACHARIAS, F. J. (1971). Propranolol in hypertension: a 5 year study. *Postgrad. med. J.*, **47**, Suppl. 75–79.

(*Received September* 15, 1972)