COMPARATIVE PHARMACODYNAMICS AND PLASMA LEVELS OF β -ADRENOCEPTOR BLOCKING DRUGS

R. GUGLER, R. KRIST, H. RACZINSKI, K. HÖFFGEN & G. BODEM

Department of Medicine, University of Bonn, 5300 Bonn-Venusberg, Federal Republic of Germany

- 1 Metoprolol (ME), pindolol (PI) and propranolol (PR) were studied in nine subjects at different doses and at 'maximum β -adrenoceptor blockade' at a defined exercise load. Exercise tests were performed after each dosing period; isoprenaline stimulation was studied at the highest dose level.
- 2 ME and PR reduced heart rate at rest with most doses tested, while PI had no effect on resting heart rate.
- 3 Exercise heart rate was reduced with the smallest daily doses (ME 75 mg; PI 7.5 mg; PR 60 mg), and maximum reduction was from 163 to 116 beats/min (ME), 124 (PI) and 115 (PR) beats/min with daily doses of 242, 23 and 233 mg, respectively.
- 4 Resting blood pressure was not significantly affected by any β -adrenoceptor blocker dose, but exercise induced blood pressure decreased from 166 to 130 (ME), 138 (PI) and 131 (PR) mm Hg, respectively.
- 5 Mean plasma concentrations at 'maximum β -adrenoceptor blockade' were 158 (ME), 24 (PI) and 159 (PR) ng/ml without significant differences in the plasma level variation between β -adrenoceptor blockers.
- 6 Isoprenaline doses required to increase heart rate by 30 beats/min were 3.8 μ g (control), 22 μ g (ME), 458 μ g (PI) and 200 μ g (PR), respectively. The differences may be due to different ratios of β_1 : β_2 activity of the β -adrenoceptor blockers tested.

Introduction

β -adrenoceptor blocking agents are now generally accepted as effective drugs for the management of hypertension, of angina pectoris, and of several forms of cardiac arrhythmias (Black & Prichard, 1973; Simpson, 1974; Singh & Jewitt, 1977). While the various β -adrenoceptor blocking drugs differ in some pharmacological properties, they are assumed to be equally effective if administered in equipotent doses. It is not clearly understood whether and to which extent different types of β -adrenoceptor blockers differ in their pharmacodynamic activities when comparable doses are given to the same individual. It was the object of this study to establish whether cardioselectivity or intrinsic sympathomimetic activity of a β -adrenoceptor blocker are associated with specific results in healthy subjects when common tests to evaluate β -adrenoceptor blockade are carried out using increasing doses and a multiple dose regimen of the β -adrenoceptor blocker in each individual. The therapeutic situation in which equipotency of the drugs was assumed to allow comparison of the β -adrenoceptor blockers was 'maximum β -adrenoceptor blockade' at a defined exercise load. Plasma concentrations of β -

adrenoceptor blockers were determined at all dose levels to provide information on the dose-concentration relationship.

Methods

Subjects

Nine healthy volunteers (six men, three women) participated in the studies after giving informed consent. Age range was 21 to 30 years, and body weight was between 53 and 81 kg. They received no other medication for at least 2 weeks before the study and during the study period. Subjects were judged healthy after a routine clinical history and physical examination. They all had normal chest films, normal ECG tracings and normal routine laboratory tests.

Drugs and general procedure

The β -adrenoceptor blockers used in the study, their pharmacological properties and the doses administered are listed in Table 1. Metoprolol represents the cardioselective (β_1 -selective) β -

adrenoceptor blocker, pindolol is an antagonist with intrinsic sympathomimetic activity (ISA), and propranolol is a nonselective β -adrenoceptor blocker without ISA, but with considerable membrane stabilizing (quinidine-like) activity.

A randomised cross-over study design was used. During a control period of at least 8 days all subjects performed their exercise test (see below) a minimum of five times on separate days until consistency of at least three tests showed us that subjects were familiarized with the test situation and no training phenomenon would affect the results. Isoprenaline stimulation (see below) was performed once in the control period. Subjects were allocated to one of the following treatment sequences: metoprolol – pindolol – propranolol; pindolol – propranolol – metoprolol; propranolol – metoprolol – pindolol.

Each β -adrenoceptor blocker was administered with increasing doses (see Table 1) until 'maximum β -adrenoceptor blockade' was achieved. Each dose was given three times daily (07.00h; 15.00h; 23.00h) over a period of 2 days (six doses). The test programme was done approximately 4 h after the afternoon dose and the subject was then placed on the next (higher) β -adrenoceptor blocker dose. When the final dose period of one antagonist was reached isoprenaline stimulation was performed in addition to the exercise test. Five days were allowed to elapse before the subject was started on the next β -adrenoceptor blocker. After each dosing period of all drugs a blood sample (12 ml) was also obtained for determination of the actual plasma concentration of the drug.

Heart rate and blood pressure at rest and exercise

Each test was preceded by a 20 min resting period, and heart rate and systolic blood pressure were subsequently recorded every minute until three subsequent readings were constant.

The exercise test was performed on a treadmill tilted at a 10° angle. During the first session in the control period the treadmill speed was increased stepwise every 4 min by 1 km h⁻¹ until an

individual work load was reached that produced a heart rate increase to just above 150 beats/min. Heart rate was determined by measuring RR distances on a continuous ECG tracing after 4 min of the maximum exercise work load. Systolic blood pressure was measured manually after 4 min of the exercise test.

Maximum β -adrenoceptor blockade

'Maximum β -adrenoceptor blockade' was assumed when by subsequent dose increase of the β -adrenoceptor blockers no further reduction of exercise tachycardia was observed. Heart rate and blood pressure tests at rest and exercise were based on results from the dose preceding the final one.

Isoprenaline stimulation

Isoprenaline stimulation was performed during the control period and after the final dosing period (one dose beyond 'maximum β -adrenoceptor blockade') of each β -adrenoceptor blocker using the technique of intermittent bolus injection (George, Conolly, Fenyvesi, Briant & Dollery, 1972). Increasing doses of isoprenaline were administered into a saline infusion, starting at 0.1 μ g and always doubling the preceding dose, and the maximum post-injection increase in heart rate was recorded. The isoprenaline dose was determined which produced an increase by 30 beats/min, but the maximum dose was chosen not to exceed 500 μ g because of unpleasant sensations in some subjects.

Plasma concentrations

Plasma samples were obtained after resting in each test period and were analysed for the β -adrenoceptor blocker concentrations by using a fluorometric assay for pindolol (Pacha, 1969), and by gas liquid chromatographic assays with electron capture detection each for metoprolol (Ervik, 1975) and propranolol (Di Salle, Baker, Bareggi, Watkins, Chidsey, Frigerio & Morselli, 1973). The assays

Table 1 Pharmacological properties of metoprolol, pindolol and propranolol, and doses administered three times daily over two days each.

	β -adrenoceptor blocking potency (propranolol = 1)	β_1 -selectivity	Intrinsic sympathomimetic activity	Membrane stabilizing activity	Doses (mg)
Metoprolol	1	+	—	+	25, 50, 75, 120
Pindolol	6	—	++	+	2.5, 5, 7.5, 10
Propranolol	1	—	—	++	20, 40, 80, 100

+ = effect present; ++ = marked effect.

Figure 1 Heart rate at rest (bottom line) and during exercise (top line) during the control period and at the end of each dosing period with the different doses of β -adrenoceptor blockers.

$n=9$, except 100 mg metoprolol (6); 10 mg pindolol (7); 120 mg propranolol (6).

(* $P < 0.05$ compared to control)

were sensitive enough to detect 4 ng pindolol, 5 ng metoprolol and 10 ng propranolol/ml of plasma, respectively.

Statistical methods

Data are commonly given as mean $\pm$ s.d. Friedman's test was used for statistical analysis of differences between β -adrenoceptor blockers, and of differences between doses of each β -adrenoceptor blocker.

Results

The doses of the β -adrenoceptor blockers at 'maximum β -adrenoceptor blockade' at a defined exercise load, the resting and the exercise induced heart rate, and the systolic blood pressure at rest and after exercise in the control period and at maximum β -adrenoceptor blockade are illustrated in Table 2.

About equal doses of metoprolol and propranolol of around 80 mg three times daily were required to produce a maximum effect, whereas the corresponding pindolol dose was about one tenth of the other β -adrenoceptor blockers.

The heart rate at rest appeared reduced with all metoprolol and propranolol doses used, but the difference was only significant for the two higher (80 and 120 mg) doses of propranolol, whereas significance was found with all but one (25 mg) of the metoprolol doses (Figure 1). Pindolol did not affect resting heart rate in any of the doses tested. Resting heart rate at 'maximum β -adrenoceptor blockade' was about equally reduced with metoprolol and propranolol to a low value around 60 beats/min, but remained essentially unchanged with pindolol (Table 2).

Exercise induced tachycardia was 163 ± 6 beats/min in the pretreatment period, and was reduced to a similar extent, though not significantly, by the smallest dose of each β -adrenoceptor blocker used (Figure 1). While subsequent increase of doses produced a larger effect with propranolol and metoprolol, changes between the first pindolol dose and higher doses were only minimal. At 'maximum β -adrenoceptor blockade' exercise heart rate was reduced by about 30% by metoprolol and propranolol, whereas reduction was smaller (25%) for pindolol (Table 2).

Systolic blood pressure at rest decreased slightly but insignificantly with the smallest β -adrenoceptor blocker doses of metoprolol and propranolol, but systolic pressure was never below a mean of 105 mm Hg independent of the doses (Figure 2). Resting blood pressure reduction was less with pindolol without a difference between the doses tested. Systolic blood pressure reduction at 'maximum β -adrenoceptor blockade' showed a similar reaction to that described for the higher doses of the β -adrenoceptor blockers in Figure 2 (Table 2).

Systolic blood pressure during exercise was 166 ± 13 mm Hg in the pretreatment period, and was

Table 2 Doses of the β -adrenoceptor blockers at 'maximum β -adrenoceptor blockade', resting and exercise induced heart rate (beats/min), and systolic blood pressure at rest and during exercise in the pretreatment period (control) and at 'maximum β -adrenoceptor blockade' with metoprolol, pindolol and propranolol.

Medication	Dose (mg three times daily)	Resting heart rate (bpm)	Exercise heart rate (beats/min)	Resting blood pressure (mm Hg)	Exercise blood pressure (mm Hg)
Control	—	73 ± 10	163 ± 6	119 ± 7	166 ± 13
Metoprolol	80.5 ± 32.5	$58 \pm 6^*$	$116 \pm 8^*$	112 ± 8	$130 \pm 22^*$
Pindolol	7.5 ± 1.7	70 ± 10	$124 \pm 4^*$	118 ± 7	$138 \pm 13^*$
Propranolol	77.7 ± 32.3	61 ± 8	$115 \pm 8^*$	108 ± 11	$131 \pm 23^*$

* Significantly different from control period

Figure 2 Systolic blood pressure at rest (bottom line) and during exercise (top line) during the control period and at the end of each dosing period with the different doses of β -adrenoceptor blockers. $n=9$, except 100 mg metoprolol (6); 10 mg pindolol (7); 120 mg propranolol (6). (Δ : $P < 0.05$ compared to control)

Figure 3 Dose-response curves for the isoprenaline stimulation in the control period (CO) and under 'maximum β -adrenoceptor blockade' with metoprolol (ME), propranolol (PR) and pindolol (PI). Curves shown for two representative subjects.

reduced by about 20 mm Hg by the smallest dose of each of the β -adrenoceptor blockers tested (Figure 2). Subsequent doses led to stepwise further reduction of blood pressure to a low level between 123 and 138 mm Hg at the highest doses (10 to 24% reduction). The

Figure 4 Isoprenaline doses required to produce heart rate increase by 30 beats/min in the control period and under 'maximum β -adrenoceptor blockade' with metoprolol, pindolol and propranolol.

highest pindolol dose produced even less reduction of exercise blood pressure compared to the preceding dose (difference only tested for those 6 subjects treated with the highest dose). At 'maximum β -adrenoceptor blockade' systolic blood pressure was reduced to about 130 mm Hg with metoprolol and propranolol, and to 138 mm Hg with pindolol (Table 2).

The dose response relationship for the isoprenaline stimulation before treatment and at 'maximum β -adrenoceptor blockade' with each drug is shown for two representative subjects in Figure 3. The pattern of changes between the drugs was identical in all subjects; the curves were shifted to the right and the sequence was: control – metoprolol – propranolol – pindolol. Isoprenaline doses needed to produce a 30 beats/min heart rate increase were $3.8 \pm 3.0 \mu\text{g}$ in the control period, $22 \pm 9 \mu\text{g}$ for metoprolol, $200 \pm 140 \mu\text{g}$ for propranolol, and $458 \pm 199 \mu\text{g}$ for pindolol (Figure 4), resulting in a dose ratio of the β -adrenoceptor blockers of 1:9:21.

The plasma concentrations determined at 'maximum β -adrenoceptor blockade' are listed on Table 3. Concentrations were nearly identical for metoprolol and propranolol, but were only one seventh for pindolol. The coefficient of variation was 42% for

Table 3 Plasma concentrations (ng/ml) of metoprolol, pindolol and propranolol at 'maximum β -adrenoceptor blockade'.

Mean	158	24.2	159
s.d.	67	11.0	91
Range	59–267	10.0–47.5	46–355

Figure 5 Plasma concentrations obtained 4 h after the final dose of each dosing period with the various doses of a) metoprolol, b) pindolol and c) propranolol.

metoprolol, 45% for pindolol, and 57% for propranolol.

The plasma level variation for the individual doses of β -adrenoceptor blockers was between 40 and 90%, and was not significantly different between the three drugs (Figure 5).

Discussion

The introduction of an increasing number of β -adrenoceptor blocking agents has raised the question whether the pharmacological properties of the individual β -adrenoceptor blockers are of clinical significance for a differential therapy. While there is common consent that some side effects, such as airway obstruction, bradycardia or Raynaud's phenomenon differ with different β -adrenoceptor blockers (Gibson, 1977), they all are thought to be equally effective in their primary indications (hypertension, angina pectoris, cardiac arrhythmias), if given in adequate doses (Waal-Manning, 1976). A comparison of different types of β -adrenoceptor

blockers at equipotent doses was attempted in this study, whereby 'maximum β -adrenoceptor blockade' defined as the maximum reduction of exercise tachycardia was chosen as a measure for equal effectiveness. The β -adrenoceptor blockers were tested in the steady state situation which with a plasma half-life of less than 6 h should have been achieved after 2 days (Johnsson & Regardh, 1976). This design was preferred to the single dose experiment since differences in the pharmacokinetics of β -adrenoceptor blockers (half-life, first-pass elimination, interindividual variation in plasma levels) do not permit conclusions for the clinical practice from single dose data. Plasma levels 4 h after the dose are taken in the middle of one dosing interval, when the peak plasma concentrations during one dosing interval should occur, but drug effects may be smaller immediately before the next dose. Thus, if one attempts 'maximum β -adrenoceptor blockade' as defined in this study during the entire dosing interval doses higher than 80 mg metoprolol (ME) and propranolol (PR) or 7.5 mg of pindolol (PI) three times daily would be necessary.

'Maximum β -adrenoceptor blockade' with three different types of β -adrenoceptor blockers showed the reduction in exercise tachycardia to be identical for ME and PR, and to be slightly less for PI. It was of interest that the work load employed here did not suppress exercise tachycardia below a mean level of 115 beats/min with any β -adrenoceptor blocker. These findings are in disagreement with the report of Bodem, Brammell, Weil & Chidsey (1973), where a plateau heart rate at exercise was seen with high practolol but not with high propranolol doses. In our studies mean heart rate increase was still 55 beats/min at 'maximum β -adrenoceptor blockade'. It can be concluded that intrinsic activity (ISA) and cardioselectivity do not grossly affect the extent of blockade of exercise induced tachycardia, although the presence of ISA with pindolol appeared to produce a flattening of the dose response curve, as had been shown before by McDevitt, Brown, Carruthers & Shanks (1977) when they compared oxprenolol with propranolol.

Similar conclusions can be drawn for the reduction of systolic blood pressure at exercise under 'maximum β -adrenoceptor blockade', where again PI only produced a slightly smaller response compared with the other drugs tested. Harry, Knapp & Linden (1975) who used a similar test to determine 'maximum β -adrenoceptor blockade' found heart rates of β -adrenoceptor blockers without ISA to be significantly less when compared with β -adrenoceptor blockers with ISA. Their findings may be due to the selection of drugs. On the other hand, the presence of ISA appears to be important for the effect of β -adrenoceptor blockers on resting heart rate, as metoprolol as well as propranolol produced a

significant reduction with small doses already, whereas pindolol had no such effect even at the highest dose level. No such clear differences between β -adrenoceptor blockers with respect to ISA have been demonstrated by Sowton, Daj Gupta & Baker (1975). In our healthy subjects resting heart rate was never below 60 beats/min, so that dangerous bradycardia under β -adrenoceptor blocker therapy should be rare without preexisting cardiac disease.

Resting blood pressure was not significantly altered in these healthy subjects at 'maximum β -adrenoceptor blockade'. These findings are of interest in the light of successful systolic blood pressure reduction at rest in hypertensive patients with all three β -adrenoceptor blockers in doses used in this study (Bengtsson, Johnsson & Regardh, 1975; Waal-Manning, 1970). This is probably due to the short dosing periods, since it may take 1 week or longer for a dose to exert its full antihypertensive effect. It may also be due to differences in the effects in normal and hypertensive subjects.

The β -adrenoceptor blockers investigated in the present study showed a different behaviour when their effect at 'maximum β -adrenoceptor blockade' was tested by isoprenaline stimulation as compared to the exercise test. Although isoprenaline testing was performed one dose level above the dose producing 'maximum β -adrenoceptor blockade', this should not have affected the response pattern of the different β -adrenoceptor blockers, since the percentage of dose increase was similar for all three drugs tested.

Despite a similar reduction of exercise tachycardia doses of isoprenaline required to abolish β -adrenoceptor blockade differed 20-fold between metoprolol and pindolol, while the respective ratios of equipotency were 1:9 between metoprolol and propranolol, and 1:2.3 between propranolol and pindolol. Similar findings of a relatively low potency of cardioselective β -adrenoceptor blockers in comparison to propranolol had been reported for practolol (Brick, Hutchinson, McDevitt, Roddie & Shanks, 1968) and metoprolol (Bengtsson *et al.*, 1975). These results indicate that peripheral as well as cardiac effects contribute to the isoprenaline tachycardia, since cardioselective drugs do not block the peripheral vasodilator effect of isoprenaline, and thus secondary vagal withdrawal can be expected to persist (Gibson & Sowton, 1977). Therefore, the behaviour of a β -adrenoceptor blocking drug under isoprenaline stimulation might give some information on its β_2 -activity in relation to the β_1 -activity, i.e. on its β_1 -selectivity.

A close correlation exists between the plasma levels of β -adrenoceptor blocking drugs and the β -adrenoceptor blocking effect in healthy volunteers (Gugler, Höbel, Bodem & Dengler, 1975; Johnsson & Regardh, 1976). However, attempts to correlate the plasma levels to the therapeutic effect, e.g. in hypertension, angina pectoris, cardiac arrhythmias, have been less successful and have revealed large interindividual variations. Propranolol levels between 30 and 90 ng/ml have been found in angina patients showing good therapeutic response (Pine, Favrot, Smith, McDonald & Chidsey, 1975), but plasma levels were 120 ng/ml or above in hypertensive patients responding to treatment (Chidsey *et al.*, 1975). Metoprolol levels were between 20 and 187 ng/ml in angina patients (Bengtsson *et al.*, 1975), but were between 100 and 240 ng/ml in hypertensive subjects. Mean pindolol levels of 70 ng/ml were reported in hypertensives classified as good responders (Anavekar, Louis, Morgan, Doyle & Johnston, 1975). Thus, although the plasma levels of metoprolol, pindolol and propranolol from healthy subjects under 'maximum β -adrenoceptor blockade' cannot simply be considered 'therapeutic levels' they still present evidence that levels found in angina patients may often be below maximum β -adrenoceptor blockade, while levels observed in hypertensive patients are mostly in a range where effects other than pure β -adrenoceptor blockade are encountered. An interesting finding is the wide range of plasma levels associated with β -adrenoceptor blocking activity, effective concentrations ranging from 10 to 350 ng/ml with propranolol.

Metoprolol and propranolol both exhibit a high hepatic extraction ratio and are subject to first-pass elimination in the liver (Johnsson & Regardh, 1976), which process is variable and should be responsible for the large variation of plasma levels with these drugs. In our study, however, the variation in plasma levels at different doses of propranolol was not truly different from pindolol, a β -adrenoceptor blocker with linear and consistent pharmacokinetics (Gugler & Bodem, 1978), and from metoprolol. The relationship between dose and mean plasma concentrations appeared to be linear for all three β -adrenoceptor blockers tested. These results indicate that no relevant differences exist with respect to dose finding between the three β -adrenoceptor blockers tested.

This study was supported by the Deutsche Forschungsgemeinschaft (Gu 86/4).

References

- ANAVEKAR, S.N., LOUIS, W.J., MORGAN, T.O., DOYLE, A.E. & JOHNSTON, C.I. (1975). The relationship of plasma levels of pindolol in hypertensive patients to

effects on blood pressure, plasma renin and plasma noradrenaline levels. *Clin. Exp. Pharmac. Physiol.*, **2**, 203–212.

- BENGTTSSON, C., JOHNSON, G. & REGARDH, C.G. (1975). Plasma levels and effects of metoprolol on blood pressure and heart rate in hypertension patients after an acute dose and between two doses during long-term treatment. *Clin. Pharmac. Ther.*, **17**, 400-408.
- BLACK, J.W. & PRICHARD, B.N.C. (1973). Activation and blockade of β -adrenoceptors in common cardiac disorders. *Br. med. Bull.*, **29**, 163-167.
- BODEM, G., BRAMMELL, H.L. WEIL, J.V. & CHIDSEY, C.A. (1973). Pharmacodynamic studies of beta-adrenergic antagonism induced in man by propranolol and practolol. *J. clin. Invest.*, **52**, 747-754.
- BRICK, I., HUTCHINSON, K.J., McDEVITT, D.G., RODDIE, I.C. & SHANKS, R.G. (1978). Comparison of the effects of ICI 50172 and propranolol in cardiovascular responses to adrenaline, isoprenaline and exercise. *Br. J. Pharmac.*, **34**, 127-135.
- CHIDSEY, C.A., MORSELLI, P., BIANCHETTI, G., MORGANTI, A., LEONETTI, G. & ZANCHETTI, A. (1975). Studies of the absorption and removal of propranolol in hypertensive patients during therapy. *Circulation*, **52**, 313-318.
- DI SALLE, E., BAKER, K.M., BAREGGI, S.R., WATKINS, W.D., CHIDSEY, C.A., FRIGERIO, A. & MORSELLI, P.L. (1973). A sensitive gas chromatographic method for the determination of propranolol in human plasma. *J. Chromatog.*, **84**, 347-352.
- ERVIK, M. (1975). Quantitative determination of metoprolol in plasma and urine by gas chromatography. *Acta Pharmac. Tox.*, **36 Suppl V**, 136-144.
- GEORGE, C.F., CONOLLY, M.E., FENYVESI, T., BRIANT, R.H. & DOLLERY, C.T. (1972). Intravenously administered isoproterenol sulfate dose-response curves in man. *Arch. int. Med.*, **130**, 361-364.
- GIBSON, D.G. (1977). Pharmacodynamic properties of β -adrenoceptor blocking drugs in man. In *Cardiovascular Drugs*, ed. Avery, G.S. Vol. **2**, 1-39, Sydney: ADIS-Press.
- GIBSON, D.G. & SOWTON, G.E. (1969). The use of beta-adrenergic blocking drugs in dysrhythmias. *Progr. Cardiovasc. Dis.*, **12**, 16-38.
- GUGLER, R. & BODEM, G. (1978). Single and multiple dose pharmacokinetics of pindolol. *Eur. J. clin. Pharmac.*, **13**, 13-16.
- GUGLER, R., HÖBEL, W., BODEM, G. & DENGLER, H.J. (1975). The effect of pindolol on exercise induced cardiac acceleration in relation to plasma levels in man. *Clin. Pharmac. Ther.*, **17**, 127-133.
- HARRY, J.D., KNAPP, M.F. & LINDEN, R.J. (1975). A test which may demonstrate in man intrinsic sympathomimetic activity of β -adrenoceptor blocking drugs. *Br. J. clin. Pharmac.*, **2**, 274 P.
- JOHNSON, G. & REGARDH, C.-G. (1976). Clinical pharmacokinetics of β -adrenoceptor blocking drugs. *Clin. Pharmacokin.*, **1**, 233-263.
- McDEVITT, D.G., BROWN, H.C., CARRUTHERS, S.G. & SHANKS, R.G. (1977). Influence of intrinsic sympathomimetic activity and cardioselectivity on beta adrenoceptor blockade. *Clin. Pharmac. Ther.*, **21**, 556-566.
- PACHA, W.L. (1969). A method for the fluorometric determination of 4-(2-hydroxy-3-isopropylaminopropoxy)-indole, a β -blocking agent, in plasma and urine. *Experientia*, **25**, 802-803.
- PINE, M., FAVROT, L., SMITH, S., McDONALD, K. & CHIDSEY, C.A. (1975). Correlation of plasma propranolol concentration with therapeutic response in patients with angina pectoris. *Circulation*, **52**, 886-893.
- SIMPSON, F.O. (1974). β -Adrenergic receptor blocking drugs in hypertension. *Drugs*, **7**, 85-105.
- SINGH, B.N., JEWITT, D.E. (1977). β -Adrenoceptor blocking drugs in cardiac arrhythmias. In *Cardiovascular Drugs*, ed. Avery, G.S. Vol. **2**, 119-159, Sydney: ADIS-Press.
- SOWTON, E., DAJGUPTA D.S. & BAKER, I. (1975). Comparative effects of β -adrenergic blocking drugs. *Thorax*, **30**, 9-18.
- WAAL-MANNING, H.J. (1970). Comparative studies on the hypotensive effects of beta-adrenergic receptor blockade. In *Symposium on Beta-adrenergic Receptor Blocking Drugs*, ed Simpson, F.O. p. 64. Auckland: Ciba Foundation.
- WAAL-MANNING, H.J. (1976). Hypertension: Which beta-blocker? *Drugs*, **12**, 412-441.

(Received February 1, 1980)