EFFECTS OF β -ADRENOCEPTOR AGONISTS AND ANTAGONISTS IN PATIENTS WITH PERIPHERAL AUTONOMIC NEUROPATHY

A.J. MAN IN'T VELD, F. BOOMSMA & M.A.D.H. SCHALEKAMP

Hypertension Unit,
Department of Internal Medicine I, room P434,
University Hospital Dijkzigt – Erasmus University,
Dr Molewaterplein 40,
3015 GD Rotterdam, The Netherlands

1 Four patients with orthostatic hypotension due to peripheral autonomic neuropathy were studied. The diagnosis was based on severe hypotension during 60-degrees head-up tilting and absence of the systolic pressure overshoot in phase IV of the Valsalva response. Plasma noradrenaline levels were less than 25 pg/ml in two patients and between 50 and 90 pg/ml in the remainder. Noradrenaline was unresponsive to head-up tilting in all. Heart rate did not change after atropine, 1 mg i.v., in three patients. Thus all patients had a postganglionic efferent sympathetic lesion, which was associated with an efferent parasympathetic lesion in three.

2 After propranolol 16 mg i.v. and metoprolol 8 mg i.v., heart rate did not change. After incremental doses of pindolol heart rate rose in a dose-dependent way by a maximum of 18 ± 3 beats/min at 1.6 mg i.v.

3 After treatment with pindolol, 15 mg daily divided in three doses, the patients, who were previously bedridden, were free of orthostatic symptoms and they were able to walk and stand without fainting. Before treatment intra-arterial pressure fell within 2 min from $115 \pm 8/58 \pm 6$ mm Hg to $57 \pm 2/40 \pm 2$ mm Hg after 60-degrees head-up tilting. During treatment supine arterial pressure was $142 \pm 9/81 \pm 5$ mm Hg and all patients tolerated the tilting procedure for at least ten minutes while arterial pressure fell to $98 \pm 9/56 \pm 4$ mm Hg.

4 The increase in supine mean arterial pressure from 72 ± 4 to 102 ± 4 mm Hg after 4 weeks treatment with pindolol was caused by a rise in cardiac output from 4.9 ± 0.6 to 6.8 ± 0.5 l/min. Calculated total peripheral resistance was unchanged. Heart rate had risen from 70 ± 3 to 88 ± 4 beats/min and stroke volume from 66 ± 3 to 80 ± 5 ml.

5 Infusion of isoprenaline in one of the patients showed supersensitivity for the chronotropic and vascular effects of this drug. Similar cardiac and vascular supersensitivity was observed for salbutamol. In this patient the isoprenaline dose-heart rate response curve was shifted to the right by a factor of 6, 72 h after discontinuation of pindolol. The salbutamol dose-heart rate response curve was shifted by a factor of 50.

6 These data illustrate the clinical applicability of the pharmacological principle of partial agonism; a pure antagonist has no effect and a partial agonist acts as a pure agonist when receptor occupancy is low. The observed chronotropic effects of salbutamol provide evidence for the existence of cardiac β_2 -adrenoceptors in man. Comparison between the cardiovascular responses to the non-selective β -adrenoceptor agonist isoprenaline and the β_2 -selective agonist salbutamol suggests preferential β_2 -adrenoceptor sensitisation in chronic autonomic failure, which can be reversed by treatment with the non-selective partial β -adrenoceptor agonist pindolol.

Introduction

β -Adrenoceptor blocking drugs exert their haemodynamic effects by virtue of their ability to interfere with endogenous neurotransmitter at the receptor site. Both the β -adrenoceptor antagonist and the neurotransmitter noradrenaline have affinity for β -receptors. The agonist and antagonist binding

to β -receptors is reversible and the agonist-antagonist interaction is of a so-called competitive type. If binding of a β -adrenoceptor blocker to the unoccupied receptor does not elicit an organ response, the blocker is called a *pure antagonist* (e.g. propranolol and metoprolol). Some β -adrenoceptor

blockers show weak receptor stimulating properties. This means that the receptor is blocked for endogenous noradrenaline by these drugs but the resulting loss of sympathetic tone on end-organs is partially replaced by the intrinsic sympathomimetic activity (ISA) or partial agonist activity (PAA) of the drug. These β -adrenoceptor blockers are called *partial agonists* (e.g. pindolol).

In the intact organism the ISA of a β -adrenoceptor blocker can only be estimated by comparison with the effects of a pure antagonist (Nyberg *et al.*, 1979). A way to quantify the amount of ISA of a β -adrenoceptor blocker more precisely is to compare its chronotropic effect on the heart with that of a full agonist in the catecholamine depleted, vagotomized animal. A unique clinical model to demonstrate these pharmacological principles is the patient with chronic autonomic failure. Some of these patients are catecholamine depleted and vagal tone on the heart is often absent. Here we report on the effects of the β -adrenoceptor blockers propranolol and metoprolol (without ISA) and the β -adrenoceptor blocker pindolol (with ISA), in four patients with severe postural hypotension due to a peripheral autonomic neuropathy. We also studied the effect of isoprenaline and salbutamol in one of these patients before and after treatment with pindolol. The therapeutic effects of pindolol on orthostatic hypotension in three of these patients have been reported in detail elsewhere (Man in't Veld & Schalekamp, 1981a).

Methods

Case 1

A woman aged 25 years was known to us since 1976 with autonomic neuropathy of acute onset (Hopkins *et al.*, 1974). Severe disabling orthostatic hypotension was the main feature of her disease. She had no signs of multiple system atrophy (MSA) as in Shy-Drager Syndrome.

Case 2

A man of 40 years was known to have primary hereditary amyloidosis of the Andrada type. Symptoms of autonomic failure were orthostatic hypotension, sexual impotence, diarrhoea and urine retention. Amyloid was demonstrated in biopsy specimens of liver, sural nerve and rectal mucosa.

Case 3

A man of 64 years had generalized autonomic failure for several years owing to amyloidosis accompanying

a multiple myeloma. Amyloid was demonstrated in biopsy specimens of liver, kidney and rectal mucosa.

Case 4

A woman of 72 years presented in our clinic with severe orthostatic hypotension. Extensive clinical examination and laboratory investigations revealed no cause for chronic autonomic failure. She was thought to have idiopathic peripheral autonomic neuropathy (IOH).

All patients gave their informed consent after the possible therapeutic consequences of the investigations had been explained. The patients were admitted to the metabolic ward. The diet contained 100 mmol of sodium and the patients had not taken any drugs for at least 3 weeks prior to the investigations. Studies were begun after the patients had been in the ward for 3 days. Diagnostic tests and drug infusions were carried out between 10.00 h and 14.00 h, while the patients were in the recumbent position after overnight bedrest. During these procedures blood pres-

Figure 1 Effect of 60-degrees head-up tilting on intra-arterial pressure in four patients with peripheral autonomic neuropathy before (hatched bars) and after (open bars) 4 weeks of treatment with pindolol, 15 mg daily, divided in three doses. Indicated are means and s.e. mean.

sure was measured in a radial artery. Heart rate was derived from a continuously recorded electrocardiogram.

The diagnosis of orthostatic hypotension owing to autonomic failure was verified in each patient by 60-degrees head-up tilting on a tilt table. The Valsalva response was recorded at least three times. Plasma noradrenaline concentration was measured by a sensitive radioenzymatic technique (Henry *et al.*, 1975), in the supine position and after tilting. The intactness of the efferent vagal fibres to the heart was assessed indirectly by injection of atropine, 1 mg i.v.

Two patients (cases 1 and 2) received propranolol and metoprolol i.v. in incremental doses as shown in Figure 2. Each dose step lasted 15 min. Metoprolol was given 3 days after the infusion of propranolol. All patients received pindolol i.v. The patients who had propranolol and metoprolol i.v. previously, received pindolol i.v. at least 1 week later. During infusions of the β -adrenoceptor blockers arterial pressure was measured at 5 min intervals using the Roche Arteriosonde. One patient (case 4) received a continuous infusion of incremental doses of isoprenaline and salbutamol as shown in Figure 4, before any β -adrenoceptor blocker was given. Salbutamol was infused 2 h after complete recovery from the isoprenaline infusion.

After these investigations the patients were treated with pindolol, 15 mg daily divided in three doses. After 4 weeks the patients were subjected to 60-degrees head-up tilting. Intra-arterial pressure was continuously monitored under the same conditions as

before treatment. Cardiac output was measured before and during treatment by a noninvasive radioisotope dilution method (Man in't Veld *et al.*, 1978). After 4 weeks of treatment with pindolol the drug was stopped in one patient (case 4) and the infusions of isoprenaline and salbutamol were repeated 72 h after the last dose of pindolol 5 mg.

Results

Assessment of autonomic failure

Patients 1, 2 and 3 became severely hypotensive and lost consciousness within 2 min of 60-degrees head-up tilting (Figure 1). Patient 4 remained conscious during tilting but arterial pressure fell by 59/29 mm Hg. The normal overshoot of systolic pressure in phase IV of the Valsalva response was absent in all patients. Plasma noradrenaline was below 25 pg/ml in patients 1 and 3. It was between 50 and 90 pg/ml in patients 2 and 4, which was below the lower limit of normal for age-matched normal individuals studied under similar conditions. Plasma noradrenaline was unresponsive to tilting in all patients. Atropine 1 mg i.v. caused no change in heart rate in cases 2, 3 and 4, whereas heart rate increased from 62 to 118 beats/min in case 1. Thus all patients had chronic autonomic failure. Apparently this was caused by a postganglionic efferent sympathetic lesion, in four and it was accompanied by an efferent vagal lesion in three.

Figure 2 Effects of propranolol, metoprolol and pindolol intravenously on heart rate in patients with peripheral autonomic neuropathy. Indicated are means and s.e.mean.

Infusions of propranolol, metoprolol and pindolol

No changes in heart rate and blood pressure were observed after infusion of propranolol and metoprolol in patients 1 and 2 (Figure 2). After infusion of pindolol however, heart rate increased in a dose-dependent way. At the maximum dose given, 1.6 mg, heart rate was 18 ± 3 beats/min (mean $\pm$ s.e.mean) above control whereas arterial pressure was unchanged.

Treatment with pindolol

After 1 to 3 days of treatment with pindolol, 15 mg daily, the patients were able to stand and walk without fainting. These findings were confirmed by comparing the effects of 60-degrees head-up tilting before and during treatment (Figure 1). Before treatment arterial pressure fell from $115 \pm 8/58 \pm 6$ mm Hg to $57 \pm 2/40 \pm 2$ mm Hg. After 4 weeks treatment supine arterial pressure was increased to $142 \pm 9/81 \pm 5$ mm Hg and all patients could tolerate the tilt procedure for at least 10 min without orthostatic symptoms, although arterial pressure fell to $98 \pm 9/56 \pm 4$ mm Hg. The increase in supine mean arterial pressure from 72 ± 4 to 102 ± 4 mm Hg was caused by a rise of cardiac output from 4.9 ± 0.6 to 6.8 ± 0.5 l/min. Calculated total peripheral resistance was unchanged (Figure 3). Heart rate had risen from 70 ± 3 to 88 ± 4 beats/min and stroke volume from 66 ± 3 to 80 ± 5 ml.

Effects of isoprenaline and salbutamol before and after 4 weeks of treatment with pindolol

Infusion of isoprenaline caused a dose-dependent increase in heart rate (Figure 4). Mean arterial pressure fell in a dose-dependent way and the infusion had to be stopped because of a fall in arterial pressure by 35 mm Hg at an increment of heart rate by 63 beats/min. Infusion of salbutamol also caused a dose-dependent decrease in arterial pressure but rather unexpectedly heart rate rose as with isoprenaline. When changes in heart rate were plotted against changes in mean arterial pressure, an identical relation was observed for the two β -adrenoceptor agonists, although isoprenaline was approximately ten times more potent than salbutamol (Figures 4 and 5). Infusions of these agonists were repeated after 4 weeks of treatment with pindolol, 72 h after the last dose of pindolol 5 mg. As compared with the results before pindolol, the isoprenaline dose-response curve was shifted to the right by a factor of 6 and the salbutamol curve by a factor of 50. The change in mean arterial pressure that occurred at an increase in heart rate of 25 beats/min was -8 mm Hg with isoprenaline and -23 mm Hg with salbutamol, which

Figure 3 Haemodynamic effects of pindolol, 15 mg daily, divided in three doses, in four patients with peripheral autonomic neuropathy. Indicated are means and s.e.mean. Cardiac output and stroke volume are converted to 1.73 m^2 body surface area. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

compares with -21 and -25 mm Hg respectively before pindolol treatment. Measurements of the plasma level of pindolol by high performance liquid chromatography with electrochemical detection (Dr Pacha, Sandoz, Basle) gave values of less than 100 pg/ml. Plots of changes in heart rate against changes in mean arterial pressure after treatment with pindolol clearly differentiated between the non-selective β -adrenoceptor agonist isoprenaline and the relatively β_2 -selective agonist salbutamol. As mentioned this was not the case before pindolol treatment.

Figure 4 Effects of isoprenaline (●—●) and salbutamol (■—■) on heart rate and mean intra-arterial pressure in a patient with a peripheral autonomic neuropathy, before (●, ■) and after (○, □) treatment with pindolol, 15 mg daily. The infusions of isoprenaline and salbutamol after 4 weeks treatment with pindolol were given 72 h after the last dose of 5 mg of pindolol.

Figure 5 Effects of isoprenaline (●—●) and salbutamol (○—○) on heart rate and mean intra-arterial pressure in a patient with peripheral autonomic neuropathy before and after treatment with pindolol, 15 mg daily, for 4 weeks. The infusions of isoprenaline and salbutamol after treatment were given 72 h after the last dose of 5 mg pindolol. By that time the plasma level of pindolol had fallen below 100 pg/ml.

Discussion

Agonist and antagonist actions of pindolol. Differences between patients with preganglionic and postganglionic efferent sympathetic lesions.

Propranolol and metoprolol, two pure β -adrenoceptor antagonists had no effect on heart rate in patients with peripheral autonomic neuropathy. After infusion of the partial β -adrenoceptor agonist pindolol heart rate rose in a dose-dependent way. Since plasma noradrenaline was very low in our patients, receptor occupancy by endogenous catecholamine was probably also low. This explains why a pure β -adrenoceptor antagonist had no effect, whereas a partial agonist acted as a pure agonist.

Treatment of our patients with pindolol, 15 mg daily, resulted in a dramatic relief of orthostatic symptoms. Before treatment the patients were completely bedridden. After treatment they were able to walk and stand without fainting. Similar results with pindolol in patients with IOH have now been reported by Robson (1981) and Kirkendall (1981, personal communication). In contrast, the deleterious effect of pindolol on orthostatic hypotension has been reported in five patients with chronic autonomic failure in Shy-Drager Syndrome (MSA), (Davies *et al.*, 1981a). In these patients pindolol lowered heart rate. It therefore acted as an antagonist. Robson (1981) reported on a similar antagonist effect of pindolol in a patient with chronic autonomic failure associated with Parkinson's disease. Chronic autonomic failure is not a uniform clinical entity. One has to differentiate between preganglionic sympathetic lesions and postganglionic lesions. This distinction is difficult, but it is important, because the site of the lesion determines the degree of denervation supersensitivity and hence the response to adrenoceptor stimulants (Bannister, 1979). Some biochemical and pharmacological tools can be used to differentiate between the two types of lesions. Patients with a peripheral sympathetic lesion, such as in idiopathic orthostatic hypotension (IOH) and in our patients with amyloidosis, have lower levels of noradrenaline in plasma than patients with preganglionic lesions and central nervous system involvement such as in MSA (Bannister *et al.*, 1979; Polinski *et al.*, 1981). In addition the degree of denervation supersensitivity is more pronounced in patients with IOH than in patients with MSA (Bannister *et al.*, 1979; Polinski *et al.*, 1981). Finally the responses of blood pressure and plasma noradrenaline to tyramine are different in these two types of efferent sympathetic degeneration. These facts explain why pindolol can act as an agonist in patients with a peripheral autonomic neuropathy, whereas the drug acts as an antagonist in patients with MSA. In fact pindolol can be used to

test the integrity of the postganglionic part of the efferent sympathetic pathway (Man in't Veld & Schalekamp, 1981b). The relevance of our observation is further amplified by the recent report of Robertson *et al.* (1981), who showed that clonidine, a partial α -adrenoceptor agonist was able to raise blood pressure in four patients with IOH, whereas it lowered blood pressure in a patient with a preganglionic lesion and orthostatic hypotension. Our data and those of Robson (1981) and Davies *et al.* (1981a) clearly illustrate the pharmacological principle of partial agonism. Whether or not a partial agonist expresses its agonist rather than its antagonist properties *in vivo* is determined by the number of receptors and the concentration of endogenous agonist at the receptor site. An increase in heart after intravenous administration of pindolol suggests a combination of low receptor occupancy and/or increased receptor number. If heart rate is unchanged or lowered after pindolol, autonomic failure is more likely to be due to a preganglionic efferent sympathetic lesion. Apparently, in such cases a beneficial effect cannot be expected and treatment with pindolol should not be encouraged (Davies *et al.*, 1981a).

The agonist nature of pindolol's action in our patients was further supported by two observations. Firstly the increase in supine mean arterial pressure was associated with an increase in cardiac output. Pindolol exerted both positive chronotropic and inotropic actions (Man in't Veld & Schalekamp, 1981c). Secondly after long-term treatment with pindolol desensitisation for the effect of isoprenaline and salbutamol on heart rate and arterial pressure was demonstrated. This phenomenon can only be explained by the agonist action of pindolol. It contrasts with the observation that pure β -adrenoceptor antagonists increase sensitivity for isoprenaline in subjects with intact autonomic function (Boudoulas *et al.*, 1977).

Supersensitivity to isoprenaline and salbutamol in patients with a postganglionic efferent sympathetic lesion. Reversal by pindolol.

Infusion of isoprenaline in one of our patients showed supersensitivity to both cardiac and vascular β -adrenoceptor stimulation. This patient was approximately six times more sensitive to isoprenaline than normal individuals (Vincent *et al.*, 1982). Supersensitivity to catecholamines in patients with chronic autonomic failure is well documented (Parks *et al.*, 1961; Engelman *et al.*, 1964; Bannister *et al.*, 1979; Polinski *et al.*, 1981). The nature of this supersensitivity is complex. Increased numbers of β -receptors have been reported in these patients (Hui & Connolly, 1981; Davies *et al.*, 1981b). This could explain, at least in part, their supersensitivity. Another interesting finding in our patients was the

dose-dependent increment in heart rate after salbutamol. Normally changes in heart rate after salbutamol in intact man are thought to be brought about through changes in sympathetic tone mediated by the arterial baroreflex. Such a mechanism can be ruled out in our patients since they had efferent sympathetic and parasympathetic lesions. An alternative explanation would be an increased number of cardiac chronotropic β_2 -adrenoceptors. Chronotropic β_2 -adrenoceptors have been demonstrated *in vitro* in several species including man (Carlsson *et al.*, 1972; Hedberg, 1981). Our observations *in vivo* confirms these findings.

The fact that for a given increment of heart rate changes in mean arterial pressure after isoprenaline and salbutamol were not different before treatment with pindolol, and the observation of preferential desensitization for β_2 -adrenoceptor stimulation after treatment suggest that β_1 - and β_2 -cardiovascular adrenoceptor sensitivity are independently regulated. This phenomenon also explains why pindolol did not increase arterial pressure acutely. The initial effects of the drug on cardiac β_1 - and β_2 -receptors may have

been counteracted by stimulation of vascular β_2 -receptors. The relative contribution of cardiac β_1 -receptor stimulation to the rise in arterial pressure may be increased with time.

Supersensitivity for β_1 -adrenoceptor stimulation in our patients, is probably related to low concentrations of noradrenaline at the receptor site. The supersensitivity for β_2 -adrenoceptor stimulation is more difficult to explain. We have no information on levels of plasma adrenaline in our patients. It should be noted that not only changes in receptor numbers but also changes in the affinities of β_1 - and β_2 -adrenoceptors for selective and non-selective agonists might be important (Manalan *et al.*, 1981).

Patients with chronic autonomic failure provide a unique opportunity for physiologists, pharmacologists and physicians to unravel the pathophysiology of the autonomic nervous system. Such knowledge may contribute to a better understanding of the pharmacological actions of adrenoceptor agonist and antagonist in various disease states. It may also lead to a more rational treatment of patients with autonomic failure.

References

- BANNISTER, R. (1979). Chronic autonomic failure with postural hypotension. *Lancet*, **ii**, 927–929.
- BANNISTER, R., DAVIES, B., HOLLY, E., ROSENTHAL, T. & SEVER, P. (1979). Defective cardiovascular reflexes and supersensitivity to sympathomimetic drugs in autonomic failure. *Brain*, **102**, 163–176.
- BOUDOULAS, H., LEWIS, R.P., KATES, R.E. & DALAMANGAS, G. (1977). Hypersensitivity to adrenergic stimulation after propranolol withdrawal in normal subjects. *Ann. int. Med.*, **87**, 433–436.
- CARLSSON, E., ÅBLAD, B., BRANDSTROM, A. & CARLSSON, B. (1972). Differentiated blockade of the chronotropic effects of various adrenergic stimuli in the cat heart. *Life Sci.*, **11**, 953–958.
- DAVIES, B., BANNISTER, R., MATHIAS, C. & SEVER, P. (1981a). Pindolol in postural hypotension: the case for caution. *Lancet*, **ii**, 982–983.
- DAVIES, B., SUDERA, D., MATHIAS, C., BANNISTER, R. & SEVER, P. (1981b). Beta-receptors in orthostatic hypotension. *New Engl. J. Med.*, **305**, 1017–1018.
- ENGELMAN, K., MUELLER, P.S., HORWITZ, D. & SJOERDSMA, A. (1964). Denervation hypersensitivity of adipose tissue in idiopathic orthostatic hypotension. *Lancet*, **ii**, 927–929.
- HEDBERG, A. (1981). Studies on β_1 - and β_2 -adrenoceptor mechanisms in the mammalian heart with special reference to the action of prenalterol. *Ph.D. Thesis*, University of Göteborg, Sweden.
- HENRY, B.P., STARMAN, B.J., JOHNSON, D.G. & WILLIAMS, R.H. (1975). A sensitive radioenzymatic assay for norepinephrine in tissues and plasma. *Life Sci.*, **16**, 375–384.
- HOPKINS, A., NEVILLE, B. & BANNISTER, R. (1974). Autonomic neuropathy of acute onset. *Lancet*, **i**, 769–771.
- HUI, K.K. & CONOLLY, M.E. (1981). Increased numbers of beta-receptors in orthostatic hypotension due to autonomic dysfunction. *New Engl. J. Med.*, **304**, 1473–1476.
- MANALAN, A.S., BESCH, H.R. & WATANABE, A.M. (1981). Characterization of (3 H) $\pm$ carazol binding to β -adrenergic receptors. Application to study of β -adrenergic receptor subtypes in canine ventricular myocardium and lung. *Circulation Res.*, **49**, 326–336.
- MAN IN'T VELD, A.J., WENTING, G.J., VERHOEVEN, R.P. & SCHALEKAMP, M.A.D.H. (1978). Quantitative radiocardiography by single-probe counting using 99m technetium albumin. *Neth. J. Med.*, **21**, 166–175.
- MAN IN'T VELD, A.J. & SCHALEKAMP, M.A.D.H. (1981a). Pindolol acts as beta-adrenoceptor agonist in orthostatic hypotension: therapeutic implications. *Br. med. J.*, **282**, 929–931.
- MAN IN'T VELD, A.J. & SCHALEKAMP, M.A.D.H. (1981b). Pindolol in postural hypotension; an aid for diagnosis and treatment? *Lancet*, **ii**, 1279–1280.
- MAN IN'T VELD, A.J. & SCHALEKAMP, M.A.D.H. (1981c). Pindolol acts as beta-adrenoceptor agonist in orthostatic hypotension. *Br. med. J.*, **283**, 561.
- NYBERG, G., WILHELMSSON, G. & VEDIN, A. (1979). Intrinsic sympathomimetic activity of penbutolol. *Eur. J. clin. Pharmac.*, **16**, 381–386.
- PARKS, V.J., SANDISON, A.G., SKINNER, S.L. & WHELAN, R.F. (1961). Sympathomimetic drugs in orthostatic hypotension. *Lancet*, **i**, 1133–1136.
- POLINSKI, R.J., KOPIN, I.J., EBERT, M.H. & WEISE, V.

- (1981). Pharmacological distinction of different orthostatic hypotension syndromes. *Neurology*, **31**, 1–7.
- ROBERTSON, D., GOLDBERG, M.R., HOLLISTER, A.S., WADE, D. & ROBERTSON, R.M. (1981). Clonidine raises blood pressure in idiopathic orthostatic hypotension. *Circulation*, **64** suppl. IV, 10.
- ROBSON, D. (1981). Pindolol in postural hypotension. *Lancet*, **ii**, 1280.
- VINCENT, J., MAN IN'T VELD, A.J., BOOMSMA, F., WENTING, G.J. & SCHALEKAMP, M.A.D.H. (1982). Elevated plasma noradrenaline in response to β -adrenoceptor stimulation in man. *Br. J. clin. Pharmac.*, (in press).