Br. J. clin. Pharmac. (1982), **13**, 317S–320S

β-ADRENOCEPTOR BLOCKING DRUGS: THE RELEVANCE OF INTRINSIC SYMPATHOMIMETIC ACTIVITY

W.J. LOUIS & J.J. McNEIL

Department of Clinical Pharmacology and Therapeutics, Austin Hospital, Heidelberg, Victoria 3084, Australia

1 This paper reviews the nature and clinical value of intrinsic sympathomimetic activity (ISA) as a property of β-adrenoceptor blocking drugs.

2 It suggests that ISA may reduce the incidence of certain cardiac, respiratory and peripheral vascular side effects including bronchospasm, peripheral vasospasm and rebound tachycardia and cardiac arrhythmias.

Introduction

β-adrenoceptor-blocking drugs have a number of important properties in addition to their ability to block β-adrenoceptors. These properties include intrinsic sympathomimetic activity (ISA), cardiac selectivity, membrane stabilizing activity and an ability to block α-adrenoceptors.

Intrinsic sympathomimetic activity (ISA)

ISA is a property which has, in the past, been somewhat neglected but interest has been rekindled by reports that drugs with this property are less likely to induce bronchospasm and have a lower incidence of side effects such as Raynaud's phenomena (Morgan *et al.*, 1974; Marshall *et al.*, 1976). There have also been reports that rebound cardiac arrhythmias may follow abrupt withdrawal of β-adrenoceptor-blockers with weak or absent ISA (Miller *et al.*, 1975; Ross *et al.*, 1981). Because they block catecholamine effects on the heart, most β-adrenoceptor-blocking drugs including those with ISA are negative inotropic agents.

One commonly asked question is what is the value of having a drug which both blocks and stimulates the β-adrenoceptor? However, even under resting conditions, heart muscle is under sympathetic stimulation and the complete absence of sympathetic activity may on occasion lead to bradycardia, cardiac failure and conduction defects (Svendsen *et al.*, 1979). Similarly there are suggestions that the absence of sympathetic activity in the bronchi may increase the percentage of the population developing bronchospasm and to increase the likelihood of patients with asthma developing an exacerbation of symptoms (Morgan *et al.*, 1974; Hughes *et al.*, 1976).

The first β-adrenoceptor blocking drug, dichloroisoprenaline, had potent ISA and increased the resting heart rate (Glover *et al.*, 1962). Clearly, the greater the positive inotropic action, the more likely this is to occur. However, currently available β-adrenoceptor blocking drugs with ISA, such as pindolol, oxprenolol, and alprenolol have much less stimulant activity (Table 1). The dose-response curves for the partial agonist property for these drugs is flat and the inotropic action so weak that the net effect in man is to prevent the extreme effects of β-adrenoceptor blockade, rather than to produce a positive inotropic effect. Moreover, the property does not interfere with their potency as β-adrenoceptor blocking agents as they are equally effective in blocking exercise-induced tachycardia (McNeil & Louis, 1979) it merely reduces the effects of negative inotropism on tissues such as heart and lung (Wale *et al.*, 1979; Frishman *et al.*, 1979b).

Table 1 Relative degree of intrinsic sympathomimetic activity of several commonly used beta adrenoceptor blocking drugs

Drug	Relative Degree of ISA
Dichloroisoprenaline	+++
Pindolol	++
Oxprenolol	+
Alprenolol	+
Practolol	+
Propranolol	0
Timolol	0
Metoprolol	0
Atenolol	0
Labetalol	0

0306–5251/82/130 317–04 $01.00

Positive inotropic drugs

Recently a new range of compounds which are partial agonists with significant positive inotropic properties have become available for clinical trials in various forms of cardiac insufficiency. These drugs include the cardioselective agonist dobutamine and the partial agonists prenalterol and ICI-118,587 (Tutte & Mills, 1975; Ronn *et al.*, 1980; Barlow *et al.*, 1979). Prenalterol and ICI-118,587 are structurally similar to the β-adrenoceptor blocking agents and have between 20 and 60% of the inotropic effect of isoprenaline. However, at higher doses their blocking properties become more prominent and prevent further stimulation of the heart.

In heart failure safe selective positive inotropic drugs could well be of value in improving cardiac performance. It is now possible to make partial agonists in which the threshold for weak agonist activity is lower than for the blocking effects of the drug and to grade the degree of positive inotropism by producing drugs whose blocking effects become more prominent as the plasma concentration increases. This blockade can then act as a governor on the maximal amount of sympathetic stimulation of the β-adrenoceptors. In the conscious animal such compounds produce little increase in heart rate, presumably because their administration is associated with some increase in vagal activity and their blocking properties reduce the incidence of arrhythmias. The present group of partial agonists can only be given by parenteral administration, but it is expected that orally active drugs of this type will soon become available and the hope is that they prove to be safe and effective in patients with chronic cardiac failure.

It would seem therefore, in designing a β-adrenoceptor blocking drug with or without partial agonist activity, that there is a range of options available ranging from no activation of the receptor through to full activation of the receptor. When the degree of activation is small and comparable in amount to resting endogenous sympathetic activity the term intrinsic sympathomimetic activity or ISA has been invoked. It is however, merely one end of the spectrum of partial agonism.

Extra-cardiac side-effects

The extra-cardiac side-effects of β-adrenoceptor blocking drugs include bronchospasm, aggravation of chronic bronchitis, abnormal dreams, nightmares and Raynauds disease (Frishman *et al.*, 1979b). β-adrenoceptor blocking drugs can increase the frequency and severity of hypoglycaemic episodes in patients on insulin and they have the usual incidence of gastrointestinal side-effects, weakness and tiredness. One difficulty in assessing the value of ISA in modifying the incidence of such side effects is the lack of sufficiently large clinical trials comparing drugs with and without this property.

Bronchospasm

Shortly after its introduction it was found that propranolol could cause severe bronchospasm in asthmatics (McNeill, 1964). Stimulation of β_2-adrenoceptors in normal bronchi leads to smooth muscle relaxation and reduction in adrenoceptor activity seems to aggravate asthma and may even induce asthma in some patients with little or no history of chronic respiratory problems (Morgan *et al.*, 1974). There is some evidence in both animals and humans to suggest that drugs which lack ISA are more likely to precipitate these asthmatic problems. Thus Oh *et al.* (1978) have demonstrated that during an exercise challenge patients pre-treated with propranolol show greater airways obstruction than patients treated with pindolol or oxprenolol.

In comparative clinical trials, Morgan *et al.* (1974) have reported a higher incidence of bronchospasm during treatment with propranolol and timolol, two drugs which lack ISA, than during treatment with pindolol and alprenolol, two drugs which possess ISA. In other studies (Frishman *et al.*, 1979a), patients whose lung function deteriorated on propranolol showed no deterioration with pindolol during acute and chronic treatment. McNeil & Louis (1979) compared pindolol with the cardioselective β-adrenoceptor blocking drugs atenolol and metoprolol and showed no advantage for the relatively cardioselective compounds in unselected patients.

There is controversy over the relative values of cardioselectivity on the one hand and partial agonist activity on the other in providing some protection against further airways obstruction. There is considerable evidence that the cardioselectivity of drugs such as practolol, atenolol and metoprolol is only relative and may be lost at higher therapeutic doses (Minneman *et al.*, 1979). If a patient does develop bronchospasm on a β-adrenoceptor blocking drug then there is evidence to suggest that β-adrenoceptor agonists more easily reverse the bronchospasm during treatment with a cardioselective agent. (Johnsson *et al.*, 1975; Formgren & Eriksson, 1975). However, as all these drugs are competitive antagonists larger doses of salbutamol will reverse the bronchospasm induced by the more potent non-selective agents.

These data should not be taken to mean that it is safe to use any of these particular groups of drugs in known asthmatics. All β-adrenoceptor drugs including the present range of cardioselective beta antagonists can precipitate severe bronchospasm, sometimes fatal, in asthmatics and can interfere with the drug treatment of asthma (Palmer, 1977).

Given the widespread use of this class of drugs what is of concern is the precipitation of broncho-

spasm in patients without a clearcut history of asthma. Although most patients show no deterioration in lung function during treatment with β-adrenoceptor blocking drugs, there are reports of patients with no past history of asthma developing bronchospasm on drugs without ISA and the absence of sympathomimetic activity seems to increase the risk of bronchospasm. This suggests that the presence of ISA may be an important protective property which will reduce the incidence of adverse bronchial effects of β-adrenoceptor blocking drugs in a population in which the asthmatics have been excluded from treatment. These suggestions require investigation by large scale clinical trials.

Raynaud's phenomena

Cold extremities and aggravation of the symptoms of Raynaud's phenomena and peripheral vascular disease have been reported as one of the most frequent adverse reactions associated with the use of β-adrenergic receptor blocking drugs (Zacharias *et al.*, 1972). Aggravation of peripheral vascular disease is often insidious and the patient may present with incipient gangrene of the toes, months after the commencement of therapy (Frolich *et al.*, 1969). In some cases a history of peripheral vascular disease may not be elicited because the patient cannot walk far enough to develop claudication. The mechanism of this adverse effect is not clearly understood but the fall in cardiac output and increased peripheral resistance which commonly occurs with this group of drugs, probably contributes. Drugs with ISA have smaller effects on resting cardiac output and have been reported to produce a lower incidence of cold extremities and Raynaud's phenomena (Marshall *et al.*, 1976). However, the data are not unequivocal and Raynaud's is seen with all beta adrenoreceptor antagonists. The drugs as a group are contraindicated in peripheral vascular disease.

Cardiac side-effects

All β-adrenoceptor blocking drugs slow the heart at least a little and reduce exercise induced tachycardia. Drugs such as propranolol and timolol which lack ISA do this to a larger extent than drugs like pindolol and oxprenolol which possess intrinsic sympathomimetic activity (Morgan *et al.*, 1974; McNeil & Louis, 1979). In a comparative study in hypertensive patients, metoprolol and atenolol (two cardioselective drugs which lack ISA), were shown to have a 30% incidence of significant bradycardia, defined as the development of pulse rates of less than 55 beats/min and some patients developed heart rates less than 50 beats/min. The negative inotropic properties of β-adrenoceptor blocking drugs are also known to contribute to the cardiac failure which can develop, particularly in elderly patients, during treatment with β-adrenoceptor blocking drugs. What is not certain is whether drugs with ISA which have less negative inotropic effect are less likely to induce cardiac failure.

Also of concern are reports of rebound arrhythmias occurring on withdrawal of treatment with β-adrenoceptor blocking drugs. In the New England Journal of Medicine, Miller *et al.* (1975) reported a series of 20 patients with angina treated with propranolol who subsequently stopped treatment (Miller *et al.*, 1975). Six of these patients had serious myocardial events, one died suddenly, another suffered a myocardial infarction, another developed ventricular tachycardia and three developed coronary insufficiency.

There are now a large number of reports of adverse cardiac events following cessation of therapy with β-adrenoceptor blocking drugs but virtually all have involved drugs with little or no ISA. Ross *et al.* (1981) have reported that these drugs produced hypersensitivity to β-adrenoceptors and cessation of treatment results in rebound tachycardia during exercise. Walden *et al.* (1982) have demonstrated a similar rebound tachycardia with propranolol, and atenolol but not pindolol. These data suggest that a certain level of ISA may protect against the development of withdrawal effects.

Conclusion

There is now some evidence that partial agonism is an important property of β-adrenoceptor blocking drugs and this property may be exploited to produce a new range of positive inotropic drugs. With the established β-adrenoceptor blocking drugs the level of partial agonist activity is weak and the dose-response curve for this property is flat. However, its absence appears to increase the likelihood of inducing bronchospasm, bradycardia and drugs which lack ISA appear more likely to be associated with rebound cardiac arrhythmias on cessation of treatment. The idea of a small level of hormone activity, in this case catecholamine activity being necessary to maintain normal cardiac and perhaps bronchial function is not new. It is well known that minimal doses of steroids are essential to maintain the inotropic action of cardiac muscle (Sayers & Solomon, 1960). There is now enough accumulated evidence to suggest that a minimal degree of β-adrenergic receptor stimulation is also important for normal bronchial and cardiac function and its absence increases the incidence of bradycardia and the risks of bronchospasm and rebound arrhythmias.

This work was supported by the National Health and Medical Research Council of Australia.

References

BARLOW, J.J., MAIN, B.G., MOORS, J.A., NUTTALL, A. & SNOW, H.M. (1979). The cardiovascular activity of ICI 118–587, a novel β-adrenoceptor agonist. *Br. J. Pharmac.*, **67,** 412P.

FORMGREN, H. & ERIKSSON, M.E. (1975). Effects of practolol in combination with terbutaline in the treatment of hypertension and arrhythmias in asthmatic patients. *Scand. J. resp. Dis.*, **56,** 217–222.

FRISHMAN, W., DAVIS, R., STROM, J., ELKAYAM, U., STAMPFER, M., RIBNER, H., WEINSTEIN, J. & SONNEBLICK, E. (1979a). Clinical pharmacology of the new beta-adrenergic blocking drugs Part 5 Pindolol (LB-46) therapy for supraventricular arrhythmias: a viable alternative to propranolol in patients with bronchospasm. *Am. Heart J.*, **98,** 393–398.

FRISHMAN, W., SILVERMAN, R., STROM, J., ELKAYAM, U. & SONNEBLICK, E. (1979b). Clinical pharmacology of the new beta-adrenergic blocking drugs Part 4. Adverse effects. Choosing a β-adrenoceptor blocker. *Am. Heart J.*, **98,** 256–262.

FROLICH, E.D., TARAZI, R.C. & DUSTAN, H.P. (1969). Peripheral arterial insufficiency. A complication of beta-adrenergic therapy. *J. Am. med. Ass.*, **208,** 2471–2472.

GLOVER, W.E., GREENFIELD, A.D.M. & SHANKS, R.G. (1962). Effects of dichloroisoprenaline on the peripheral vascular responses to adrenaline in man. *Br. J. Pharmac.*, **19,** 235.

HUGHES, F.C., JULIEN, D., BORIS, V. & MARCHE, J. (1976). Effects de differents beta-bloquers sur le debit expiratoire de l'asthmatique. *Therapie*, **31,** 595–603.

JOHNSSON, E., SVEDMYR, N. & THIRINGER, G. (1975). Effects of intravenous propranolol and metoprolol and their interaction with isoprenaline. *Eur. J. clin. Pharmac.*, **8,** 175–180.

MARSHALL, A.J., ROBERTS, C.J.C. & BARRITT, D.W. (1976). Raynaud's phenomenon as a side effect of beta-blockers in hypertension. *Br. med. J.*, **1,** 1498–1499.

McNEILL, R.S. (1964). Effect of a beta-adrenergic blocking agent, propranolol, on asthmatics. *Lancet*, **ii,** 1101–1102.

McNEIL, J.J. & LOUIS, W.J. (1979). A double-blind cross-over comparison of pindolol, metoprolol, atenolol and labetalol in mild to moderate hypertension. *Br. J. clin. Pharmac.*, **8,** 163S–166S.

MILLER, R.R., OLSON, H.G., AMSTERDAM, E.A. & MASON, D.T. (1975). Propranolol withdrawal rebound phenomenon. *New Engl. J. Med.*, **293,** 416–418.

MINNEMAN, K.P., HEGSTRAND, L.R. & MOLINOFF, P.B. (1979). The pharmacological specificity of beta-1 and beta-2 adrenergic receptors in rat heart and lung *in vitro*. *Mol. Pharmac.*, **16,** 21–33.

MORGAN, T.O., SABTO, J., ANAVEKAR, S.N., LOUIS, W.J. & DOYLE, A.E. (1974). A comparison of beta adrenergic blocking drugs in the treatment of hypertension. *Postgrad. med. J.*, **50,** 253–259.

OH, V.M.S., KAYE, C.M., WARRINGTON, S.J., TAYLOR, E.A. & WADSWORTH, J. (1978). Studies of cardioselectivity and partial agonist activity in β-adrenoceptor blockade comparing effects on heart rate and peak expiratory flow rate during exercise. *Br. J. clin. Pharmac.*, **5,** 107–120.

PALMER, K.N.V. (1977). Respiratory side effects of beta-blockers. *Br. med. J.*, **1,** 841C.

RONN, O., FELLENIUS, E., GRAFFNER, C., JOHNSSON, G. LUNDBORG, P. & SVENSSON, L. (1980). Metabolic and haemodynamic effects and pharmacokinetics of a new selective $beta_1$-adrenoceptor agonist, prenalterol, in man. *Eur. J. clin. Pharmac.*, **17,** 81–86.

ROSS, P.J., LEWIS, M.J., SHERIDAN, D.J. & HENDERSON, A.H. (1981). Adrenergic hypersensitivity after beta-blocker withdrawal. *Br. Heart J.*, **45,** 637–42.

SAYERS, G. & SOLOMON, N. (1960). Work performance of a rat heart-lung preparation: standardisation and influence of corticosteriods. *Endocrinology*, **66,** 719–730.

SVENDSEN, T.L., HARTLING, O., TRAP-JENSEN, J. (1979). Immediate haemodynamic effects of propranolol, practolol. *Eur. J. clin. Pharmac.*, **15,** 223–228.

TUTTLE, R. & MILLS, J. (1975). Development of a new catecholamine to selectively increase cardiac contractility. *Circulation Res.*, **36,** 185–186.

WALDEN, R.J., BHATTACHARJEE, P., TOMLINSON, B., CASHIN, JEANETTE, GRAHAM, B.R. & PRICHARD, B.N.C. (1982). The effect of intrinsic sympathomimetic activity on β-receptor responsiveness after β-adrenoceptor blockade withdrawal. *Br. J. clin. Pharmac.*, **13,** 359–364.

WALE, J.L., AUSTIN, M., CONWAY, J. & REEVES, M. (1979). The influence of the intrinsic sympathomimetic activity of -adrenoceptor agonists on haemodynamic effects in anaesthetized dogs. *Clin. exp. Pharmac. Physiol.*, **6,** 11–19.

ZACHARIAS, J., COWEN, K.J., PRESCOTT, J. & VICKERS, J. (1972). Propranolol in hypertension – a study of long term therapy. 1964–1970. *Am. Heart J.*, **83,** 755–761.