Measurement of partial agonist activity in man and its therapeutic relevance

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Historical Perspective

The dichlorinated analogue of isoproterol was found to have both competitive inhibitory (antagonist) effects and stimulating (agonist) activity on beta-adrenoceptors [1]. Consequently, dichloroisoproterenol (DCI) was the first chemical to be identified as a beta-adrenoceptor blocker With intrinsic sympathomimetic activity (ISA), a term used to describe the partial agonist activity (PAA) of a drug exerting both agonist and antagonist effects on beta-adrenoceptors.

Pronethalol, the first commercially available beta-blocker, exhibited a mild degree of PAA and subsequent drugs with this property include alprenolol, practolol, pindolol, oxprenolol, bunitrolol and bucindolol.

The classical studies of partial agonist activity have been performed in animals which have been adrenalectomized or pretreated with reserpine or syrosingopine to deplete endogenous catechomalines and which have been pithed and/or vagotomized to limit reflex responses [2-4]. In these models, beta-blockers devoid of PAA do not influence heart rate, whereas beta-blockers with PAA increase heart rate to a variable extent.

Although there are apparent inter-species differences in PAA, the apparent order of agonist activity of different beta-blockers is: DCI > pindolol > practolol > oxprenolol > pronethalol > alprenolol > acebutolol.

There is a gap between the maximum effect on heart rate of isoproterenol and the maximum effect of each partial agonist which is though to reflect a balance between agonist and antagonist activity [5]. The increases in heart rate appear to be mediated by beta-adrenoceptors stimulation since they can be competitively antagonized by propranolol which does not exert PAA.

Measurements of PAA in man

The evaluation of PAA in man is complicated by the necessity to study the intact specimen! Nevertheless, careful comparison of the cardiovascular responses of healthy volunteers and patients to different beta-adrenoceptor blocking drugs has made it possible to measure the effect of PAA in man and to comment on its therapeutic relevance.

Differences in the level of sympathetic tone apparently influence the response to different beta-blockers. Propranolol has little effect on resting heart rate but is capable of reducing standing hear rate from approximately 100 beats per minute to 80 beats per minute. Pindolol, on the other hand, exerts little effect on standing heart rate [6,7]. In patients with disautonomia the PAA of pindolol results in an actual increase in heart rate and blood pressure [8].

The reduction of exercise heart rate is a well established method of evaluating cardiac beta-adrenoceptor blocking activity in man. The dose-response relationships of a large number of beta-block in drugs on exercise heart rate have been studied in healthy young adults [6,9-14]. Only three consistent differences have been noted between the dose response curves. The drugs differ in their potencies, in the steepness of their dose-response relationship and their maximum effects on exercise heart rate. Those beta-blockers with PAA exhibit flatter dos and concentration-response curves and reduce exercise heart rate to a lesser extent.

The differences between beta-blockers with partial agonist activity and those without PAA can be demonstrated further by evaluation of interactions between these two classes of drugs [13]. In a recent study, we have examined the interaction between metoprolol and pindolol [15]. Metoprolol reduced stand in heart rate 97 to 78 beats per minute whereas pindolol had no effect on this measurement. Metoprolol reduced exercise heart rate from 160 beats per minute to 111 beats per minute compared with 121 beats per minute following pindolol. The standing and exercise heart rates following pindolol were unchanged when metoprolol was added to pindolol. However when pindolol was added to metoprolol, the lower standing and exercise heart rates following metoprolol were increased to values similar to those observed following pindolol alone.

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Relevance of PAA in man

Although partial agonist activity can be readily demonstrated in animal and human models such as those discussed above, the apparent lack of any therapeutic difference between beta-blockers in the management of angina pectoris, hypertension and cardiac arrhythmias has lead many investigators, including McDevitt [16], to question the clinical importance of this property. Wall-Manning and Simpson[17] even went so far as to suggest that partial agonist activity might be responsible for a dose-dependent reduction of the anti-hypertensive action of beta-adrenoceptor blocking drugs with PAA, a conclusion which was convincingly refuted by Koldsland [18].

The work of Atterhog, Duner and Pernow [19] drew attention to possible differences in the hemodynamic responses of pindolol. In contrast to the usual decrease in cardiac output and consequent reflex in crease in peripheral resistance following propranolol, these investigators noted that pindolol exerted its anti-hypertensive action by reduction peripheral resistance while maintaining cardiac output essentially unchanged from control observations. Other workers have also demonstrated a lack of reduction of resting cardiac output or at least a lesser reduction of cardiac output following treatment with beta-blockers with PAA. Svendsen, Hartling and Trap-Jensen [2O] compared the effects of propranolol and atenolol (both devoid of PAA) and pindolol, practolol and ICI 89406 (all of which possess PAA) on heart rate and cardiac output in healthy volunteers. Pindolol, ICI 89406 and practolol had minimal effects on heart rate or cardiac output whereas comparable beta-blocking doses of propranolol and atenolol reduced cardiac output from 20 to 30 percent.

Franciosa, Johnson and Tobian [2l] demonstrated by standard invasive techniques that there was a lack of reduction of cardiac output in mildly hypertensive patients who received oxprenolol which also has PAA. Oxprenolol actually increase stroke volume by 22 ml/beat at peak exercise but cardiac output was not changed because of the concurrent slowing of heart rate. The duration of exercise and oxygen consumption were unchanged following oxprenolol therapy. At peak exercise, propranolol reduced cardiac output by 1.7 L/min, a factor attributed by Franciosa and is colleagues to the 25 percent reduction in the duration of exercise following propranolol.

Heikkila and Nieminen [22] examined left ventricular size and contractility echoventriculography. In healthy subjects they found a 20 percent increase in left ventricular size following metoprolol and a corresponding 15 percent reduction in a contraction index assessed from 8 standard segments around the left ventricular wall. These observations were supported by measurements of contractility in the ischaemic myocardium of patients who had suffered a previous myocardial infarction. Again metoprolol tended to depress mechanical function in the healthy myocardium while exerting only minimal improvement in the contractility of the ischaemic areas. Pindolol did not increase left ventricular size or depress the composite contraction index in healthy individuals. In patients with myocardial infarction, pindolol improved the contractility in the ischemic area.

Taylor and is colleagues [23] have administered a variety of beta-blockers to patients who had recently suffered an acute myocardial infarction. They found a clear difference between the hemodynamic effects of oxprenolol and practolol (with PAA) and two other beta-blockers which were devoid of this property (metoprolol and propranolol). Pulmonary wedge pressure (PCWP) during exercise did not change significantly following oxprenolol and practolol whereas it increased after administration of the other drugs and there was a correspondingly great fall in cardiac index after propranolol and metoprolol.

The relationship between intrinsic sympathomimetic activity and the hemodynamic responses to beta-adrenoceptor antagonists has been extensively reviewed by Man in't Veld and Schalekamp [24] who have brought together a unifying concept of the role of partial agonist activity in the therapy of hypertension. They conclude that certain observations are consistent with ISA. Beta-blockers with partial agonist activity do not influence plasma rennin concentrations nor do they significantly influence plasma noradrenaline concentrations. Drugs without ISA decrease heart rate, reflexly increase peripheral vascular resistance in the short term and then perhaps by pre-junctional beta-blockade cause a subsequent reduction in peripheral resistance with a trend to ward normalization of cardiac output. Partial agonist drugs on the other hand maintain cardiac out put but exert their anti-hypertensive effect by lowing the pathologically increased peripheral vascular resistance of hypertension.

More direct evidence of the peripheral vascular effects of pindolol comes from the work of Ohlsson and Lindell [25] who studied the effects of replacing their beta-blockers with pindolol in patients who were experiencing cold hands. There was subjective improvement in 8 of 9 patients and an average improvement of almost 30 percent in hand blood flow measured by plethysmography. Intra-arterial infusion of pindolol in doses which produce plasma concentrations comparable with those following conventional oral doses has also been shown to produce arterial vasodilatation of 20-25 percent (Aellig 1983, personal communication).

What then are the factors which influence the clinical actions of a partial agonist such as pindolol in a particular patient? It is evident that the level of sympathetic tone is important. If a tissue contains predominantly beta-1 receptors and sympathetic tone is high, pindolol exerts predominantly beta-1 adrenoceptor blocking activity, e.g. reducing exercise heart rate in a patient with angina pecto-

ris. If beta-2 adrenoceptor tone in a tissue is low, pindolol exerts a beta-2 adrenoceptor stimulant effect, e.g. vascular relaxation with vasodilatation in skeletal muscle arteries in a hypertensive patient. The fact that virtually all tissues contain a mixture of beta-1 and beta-2 receptors in variable proportions may account for the differences which have been reported between pindolol and other beta-adrenoceptor blocking drugs on heart rate, respiratory function [26], glucose tolerance [27] and plasma lipids [28].

Our increased knowledge of the pharmacological profile of pindolol makes it easier to understand some of the older clinical observations. Pindolol is a non-specific beta-adrenoceptor antagonist. Its agonist activity, however, is exerted predominately on beta-2 adrenoceptors. Whereas its beta-1 adrenoceptor agonist activity is only 10 to 20 percent that of isoproterenol, its beta-2 adrenoceptor activity is close to the complete agonist activity demonstrated by isoproterenol.

It has become apparent that it will not be sufficient in the future to describe a drug as a partial agonist. Rather, it will behoove us to describe the drug in terms such as "non-selective beta-adrenoceptor antagonist with predominantly beta-1 adrenoceptor agonist activity", "relatively beta-1 selective beta-blocker with predominantly beta-1 adrenoceptor agonist activity" and so on.

Pindolol, a non-selective beta-adrenoceptor blocking drug with predominantly beta-2 adrenoceptor stimulant activity has unique characteristics which contribute to effective beta-adrenergic blockade when that property is desirable but limit the negative or unwanted aspects of beta-blockade such as the reduction in cardiac output and the increase in peripheral resistance which may contribute with excessive bradycardia to lethargy and easy fatigability, cold peripheries and even Raynaud's phenomenon in certain patients. If we accept that we should strive towards correcting abnormal physiology and biochemistry and avoiding causing abnormalities with our treatments, beta blockade with partial agonist activity is more effective in achieving these goals.

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