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PINDOLOL – A β-ADRENOCEPTOR BLOCKING DRUG WITH PARTIAL AGONIST ACTIVITY: CLINICAL PHARMACOLOGICAL CONSIDERATIONS

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1 Pindolol is a β-adrenoceptor antagonist equally effective on β_1- and β_2-adrenoceptors which has a relatively long duration of action. It is practically completely absorbed and, unlike most other β-adrenoceptor blockers, is only metabolized to a small extent during the first passage through the liver.

2 Pindolol possesses partial agonist activity (intrinsic sympathomimetic activity, ISA). This means that apart from blocking β-adrenoceptors it produces some stimulation. Pindolol therefore only slightly influences normal sympathetic drive at rest but effectively reduces the effects of elevated sympathetic activity.

3 Various therapeutic advantages have been attributed to the partial agonist activity of pindolol: no or only slight alterations in normal cardiac output, heart rate and peripheral blood flow occur. Peripheral resistance is reduced during chronic oral therapy. No alteration of HDL/LDL cholesterol ratio has been observed. Rebound phenomena on sudden withdrawal of therapy and bronchoconstriction in susceptible patients are less likely than with drugs devoid of ISA.

Introduction

Pindolol is a β-adrenoceptor blocking drug which is equally effective on β_1- and β_2-adrenoceptors and possesses partial agonist activity. When pindolol was introduced 12 years ago it was then one of the few β-adrenoceptor blocking drugs available. At that time most of the emphasis of pharmacological and clinical research was laid on the cardiovascular effects of β-adrenoceptor blockade as such and the place of this new type of drug in the therapeutic armamentarium for the treatment of angina pectoris, arrhythmias and hypertension. The ancillary properties like membrane stabilizing action and intrinsic sympathomimetic activity (ISA, partial agonist activity) were considered to be of minor clinical relevance. Already in 1969, however, Hill & Turner, while carrying out studies with pindolol and propranolol in healthy volunteers, found that in equipotent β-adrenoceptor blocking doses pindolol produced less reduction in resting heart rate than did propranolol. This was the first evidence of pindolol's ISA in man confirming the partial agonist activity seen in animal experiments (Clark & Saameli, 1970).

The clinical pharmacology of pindolol has recently been reviewed (Aellig, 1982). After a short summary of the most important general aspects of the clinical pharmacology of pindolol the present paper will therefore mainly deal with the effects arising from its partial agonist activity.

Like all β-adrenoceptor blocking drugs pindolol inhibits the effects of β-adrenoceptor stimulation on the heart. It therefore reduces tachycardia due to exercise or to intravenously infused isoprenaline. In these experiments pindolol is on a weight for weight basis about 20 times more potent than propranolol (Hill & Turner, 1969; Aellig, 1976a). The duration of action of pindolol is longer than that of propranolol (Aellig, 1976a), alprenolol (Olsson & Varnauskas, 1973; Aellig, 1978a), and slow-release oxprenolol (Aellig, 1978b) tested at equipotent β-adrenoceptor blocking doses.

Like most β-adrenoceptor blocking drugs pindolol is rapidly and practically completely absorbed; its maximum plasma level is reached 1.5 to 2 h after ingestion. The elimination half-life is 3–4 h, and 40% of the drug is excreted unchanged in the urine (Meier, 1977; Gugler, 1980). Unlike most other β-adrenoceptor blockers, pindolol has only a small first-pass effect (Meier & Nüesch, 1977), i.e. it is metabolized only to a small extent during the first passage through the liver. This is responsible for its

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good oral bioavailability of about 87% and small variations of plasma levels from patient to patient (Gugler & Bodem, 1978; Meier, 1977).

Pharmacodynamic studies in healthy volunteers confirmed the good systemic availability of pindolol; almost equal β-adrenoceptor blockade was measured 75 min after intravenous and 2 h after oral administration of the same doses of the drug (Aellig, 1976b).

As with other β-adrenoceptor blockers (Coltart & Shand, 1970; Carruthers *et al.*, 1974), a linear correlation was found between the logarithm of pindolol plasma levels and the pharmacodynamic effect, expressed by the reduction of exercise-induced tachycardia (Aellig, 1980). This of course applies only to measurements on the linear part of the S-shaped log dose-response curve. With higher doses of β-adrenoceptor blocking agents, as with other drugs, the log plasma level-effect curve flattens and no further increase in effect can be seen (Bobik *et al.*, 1979; Jennings *et al.*, 1981).

What is a partial agonist and what does ISA mean?

Much confusion has arisen from a misunderstanding of the pharmacological terms 'partial agonist activity' and 'intrinsic sympathomimetic activity'. It seems therefore advisable to give a brief explanation (see also Clark, 1982a). A partial agonist stimulates the receptors, but its efficacy (i.e. the maximum possible effect) is smaller than that of a full agonist. Intrinsic sympathomimetic activity (ISA) has the same meaning as partial agonist activity, but the first term is reserved for β-adrenoceptor blocking drugs.

A β-adrenoceptor blocking drug with partial agonist activity (intrinsic sympathomimetic activity) blocks β-adrenoceptors like a drug devoid of this property; however, it also provides some stimulation to the receptors. This stimulatory activity never produces a maximum effect as high as that reached with a full agonist like isoprenaline, no matter how high the doses used are. β-adrenoceptor stimulating efficacy of β-adrenoceptor blocking drugs with partial agonist activity in clinical use today is either smaller than or, in the case of pindolol, just about as high as normal resting sympathetic activity. This means that the stimulating activity of the drug totally or partly compensates for the loss of resting sympathetic drive consequent upon β-adrenoceptor blockade. Increased sympathetic stimulation, however, is reduced by a β-adrenoceptor blocking drug with partial agonist activity as much as by a β-adrenoceptor blocking drug devoid of this property. Despite the fact that no drug in clinical use today has a partial agonist activity higher than normal resting sympathetic tone, drugs with higher ISA have been developed. Examples are dichloroisoprenaline (DCI) and Sandoz 23-784, which cause tachycardia at rest. Both, however, are effective in reducing the effects of elevated sympathetic tone or of intravenously infused isoprenaline. Experiments with 23-784 have shown that this drug was in fact the most potent β-adrenoceptor blocking drug ever tested. Besides elevating resting heart rate from about 75 to 95 beats/min, an oral dose of only 0.5 mg of this drug raised the dose of isoprenaline required to increase heart rate to 120 beats/min from 8 μg/min to 349 μg/min (Aellig, 1977).

In the therapeutic dose range the partial agonist activity of pindolol is practically independent of the administered dose because the maximum stimulating activity is already reached with low doses (Clark, 1982b).

ISA and heart rate

First evidence for pindolol's ISA in man came from Hill & Turner's (1969) findings that in equipotent β-adrenoceptor blocking doses pindolol produces less reduction of resting heart rate than propranolol, which has no ISA. Because the maximum stimulating activity of pindolol is reached with rather low doses the net effect on resting heart rate is mainly related to the level of sympathetic tone. In an experiment in healthy volunteers, resting heart rate in the lying position, i.e. in circumstances where the sympathetic tone is very low, was slightly increased after pindolol, whereas in the sitting position, when sympathetic tone was higher, pindolol reduced heart rate. Propranolol reduced resting heart rate both in the sitting and in the lying position (Aellig, 1976a). Also in patients with hyperkinetic heart syndrome or hyperthyroidism, i.e. subjects with a high resting sympathetic tone, pindolol markedly reduced the elevated resting heart rate (Dufour *et al.*, 1971). However, in bedridden patients with severe orthostatic hypotension due to chronic autonomic failure, i.e. in patients with an extremely low sympathetic tone, pindolol elevated supine heart rate (Man in't Veld & Schalekamp, 1981a).

Rosenthal *et al.* (1979) found a direct linear correlation between the effect of pindolol on resting heart rate and pre-treatment heart rate. In their therapeutic study in 7062 hypertensive patients, pindolol produced a slight increase when initial heart rate was below about 65 beats/min whereas with higher heart rates reductions were observed, which were proportional to the initial value.

Carruthers & Twum-Barima (1981) studied the effects of cumulative oral doses of pindolol from 2.5 to 57.5 mg and found no difference in the effect of the different doses on resting heart rate. This shows that over a wide dose range partial agonist activity is

practically independent of the dose. During exercise sympathetic tone is high and therefore β-adrenoceptor blockers produce a reduction. Oral doses of 5 mg pindolol reduced exercise-induced tachycardia to the same extent as did 100 mg propranolol (Aellig, 1976a). It has been postulated that if the doses of β-adrenoceptor blocking drugs are increased beyond the straight part of the S-shaped log dose-response curve the maximum reduction of exercise-induced tachycardia reached with a drug having partial agonist activity would be somewhat lower than after a drug without ISA (Harry *et al.*, 1975; McDevitt *et al.*, 1977; Carruthers & Twum-Barima, 1981). This difference, however, is small and is due to the different effects on resting heart rate. Jennings *et al.* (1981) showed that the slope of the exercise level-heart rate curve was flattened to the same extent after high doses of pindolol and oxprenolol, two drugs with ISA, and timolol and metoprolol, two drugs without ISA. The maximim reduction of the exercise-induced increase in heart rate it therefore as great with drugs with ISA as with drugs without ISA. Both types of β-adrenoceptor blocking drugs, i.e. with and without ISA, have the same efficacy in the treatment of hypertension (Morgan *et al.*, 1974; McNeil *et al.*, 1979; Prichard, 1979; Waal-Manning, 1976) and angina pectoris (Arstila *et al.*, 1973; Frishman *et al.*, 1979).

Quantification of ISA

Different approaches have been used to detect and to quantitate ISA in vivo in healthy subjects or in vitro on human tissues. As discussed above, qualitative data can most easily be obtained by studying resting heart rate before and after the different drugs. A method for a quantitative estimation of ISA has been suggested by Nyberg *et al.* (1979). They measured heart rate at rest and during exercise after vagal blockade with atropine before and after administration of drugs with and without ISA. ISA was defined as the percentage by which, during maximal sympathetic stimulation and after atropinization, heart rate was less reduced by the drug with ISA, compared with propranolol (without ISA). In this way values of about 25% were obtained for pindolol (Nyberg *et al.*, 1981) and about half as much for penbutolol. The validity of the method has been questioned (Man in't Veld & Schalekamp, 1981b), but nevertheless it has permitted a quantitative comparison of the ISA of different β-adrenoceptor blocking drugs. Lima *et al.* (1981) studied the influence of acebutolol, atenolol, pindolol and timolol on cyclic AMP concentrations in human lymphocytes. They showed that of these four drugs only pindolol produced a significant increase in cAMP, which they attributed to its partial agonist activity. In another study (Lima & Turner, 1981) the same effect was confirmed with practolol.

ISA and haemodynamics

Owing to the fact that pindolol only slightly influences normal resting sympathetic tone and normal resting heart rates, a far smaller reduction in cardiac output is expected after the administration of this drug than after β-adrenoceptor blocking drugs without ISA. This has been confirmed in studies in healthy volunteers (Svendsen *et al.*, 1980) and patients with ischaemic heart disease (Svendsen *et al.*, 1981). This smaller reduction in cardiac output is thought to be responsible for smaller reflectory rise of peripheral resistance than observed after betablockers without ISA. In a study in healthy volunteers, orally administered propranolol produced a marked reduction in blood flow in the lower extremities, whereas the effects of an equipotent β-adrenoceptor blocking dose of pindolol did not differ from those of placebo (Aellig, 1979). In a therapeutic cross-over study McNeil *et al.* (1979) encountered side-effects of cold extremities more frequently during therapy with metoprolol than with pindolol. Ohlsson & Lindell (1981) reported that in a cross-over study in patients complaining of cold extremities during therapy with atenolol or propranolol hand blood flow was significantly increased during treatment with pindolol and subjective symptoms improved. In haemodynamic studies in patients with essential hypertension pindolol was found to reduce peripheral resistance during chronic oral therapy, contrary to results obtained with propranolol and metoprolol (Atterhög *et al.*, 1977; Svensson *et al.*, 1981; Tsukiyama *et al.*, 1976).

Renal haemodynamics were not affected either during chronic oral therapy with pindolol (Boner *et al.*, 1980; Wilcox *et al.*, 1981).

A venodilator effect of pindolol has been postulated by Rumboldt *et al.* (1975) after acute *in vivo* studies on superficial human veins. Wilcox *et al.* (1981), on finding that in hypertensive patients treated with pindolol blood volume showed some increase without a concomitant rise in body weight, total body water or extracellular fluid volume, postulated that partial agonist activity might produce some reduction in blood pressure by causing capacitance vessel dilatation. Atterhög *et al.* (1976) confirmed a reduction of venous tone in a study with chronic oral therapy on patients with essential hypertension. This effect, however, was only small and, as with other β-adrenoceptor blocking drugs, no signs of orthostatic hypotension have been found during therapy with pindolol.

Other effects attributed to ISA

Metabolic effects

Reductions in the ratio of HDL cholesterol to LDL cholesterol considered undesirable (Yaari *et al.*, 1981) were observed after the chronic administration of β-adrenoceptor blocking drugs without ISA like sotalol (Lehtonen & Viikari, 1979) and propranolol (Leren *et al.*, 1980; Tanaka *et al.*, 1976). Therapy with pindolol produced no such effect (Leren *et al.*, 1981); the subject of the influence of β-adrenoceptor blocking drugs on plasma lipids is discussed more extensively by Miettinen *et al.* (1982), Pasotti (1982) and Lehtonen (1982) in the same issue of this journal.

Schlüter *et al.* (1982) studied the effects of pindolol, propranolol and metoprolol on insulin-induced hypoglycaemia in healthy volunteers. They found that insulin-induced hypoglycaemia was somewhat smaller after pindolol and metoprolol compared with placebo and propranolol. After metoprolol and propranolol, the two drugs without ISA, there was a significant decrease of serum insulin compared with placebo, an effect not observed after pindolol, the drug with ISA.

Whithdrawal symptoms

Withdrawal symptoms have been reported after suddenly stopping therapy of angina pectoris or hypertension with β-adrenoceptor blocking drugs. This has been attributed to an increase in β-adrenoceptor density during chronic β-adrenoceptor blockade (Aarons *et al.*, 1980). During the administration of β-adrenoceptor stimulant drugs the opposite effect, i.e. a down-regulation of β-adrenergic receptors, has been found. It was therefore postulated that β-adrenoceptor blocking drugs with partial agonist activity would produce no or only smaller alterations in receptor density during chronic oral therapy. These drugs would thus be less likely to give rise to rebound phenomena on sudden withdrawal. Experimental studies with pindolol in healthy volunteers (Walden *et al.*, 1982) and patients with essential hypertension (Rangno, 1982; Lang *et al.*, 1982) confirmed such a difference in the occurrence of withdrawal symptoms between pindolol and β-adrenoceptor blocking drugs devoid of ISA. The subject of the withdrawal of β-adrenoceptor blocking drugs has been reviewed by Prichard & Walden (1982).

Lung function

Oh *et al.* (1977) have postulated that partial agonist activity may be more important in preventing air flow obstruction in susceptible subjects than cardioselectivity. The subject of partial agonist activity and lung function is discussed separately in the same issue of the journal (Louis, 1982; Dorow, 1982; Ruffin *et al.*, 1982).

Conclusions

Pindolol is a potent antagonist at β_1- and β_2-adrenoceptors; owing to its small first-pass-effect it has a high systemic availability. Pindolol's partial agonist activity is sufficient to compensate for the loss of resting sympathetic drive resulting from blockade of β-adrenoceptors. Pindolol therefore does not influence or only slightly reduces normal resting heart rate and cardiac output. Thus, no undesirable compensatory increase in peripheral resistance occurs. In acute experiments no reduction of peripheral blood flow was observed. During chronic oral therapy with pindolol, peripheral resistance was found to be reduced, suggesting that the drug exerts its antihypertensive effect in a pathophysiologically desirable way (Weil & Waite, 1982). Other therapeutic advantages of pindolol have been attributed to its partial agonist activity, for instance that it is less likely to give rise to rebound phenomena on sudden withdrawal or to induce bronchoconstriction in susceptible patients and that no unwanted alterations in the ratio between HDL and LDL cholesterol are observed.

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