CARDIAC DOSE-RESPONSE RELATIONSHIPS OF ORAL AND INTRAVENOUS PINDOLOL

S. GEORGE CARRUTHERS

University Hospital, University of Western Ontario
London, Ontario, Canada

- 1 The dose-response curve of pindolol on exercise heart rate has been constructed from observations in healthy male subjects studied 2 h after oral doses of pindolol 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 5 mg, 10 mg and 20 mg. This dose-response curve has been compared with historical controls who received atenolol, oxprenolol, practolol, propranolol and sotalol.
- 2 The dose-response curves differ in the relative potency of the drug, the maximum reduction of heart rate and possibly in the slope of the curves. Pindolol is extremely potent. At doses which produce 15% reduction of exercise heart rate, the relative potencies of the drugs were: pindolol (1), atenolol (1:21) oxprenolol (1:19), practolol (1:44), propranolol (1:25) and sotalolol (1:160). The maximum effects produced by pindolol, oxprenolol and practolol were less than those of the other β -adrenoceptor blocking drugs, an effect which is probably the result of their partial agonist activity.
- 3 Following intravenous pindolol 0.005, 0.01, 0.02 and 0.045 mg/kg the reduction of exercise heart rate and duration of action were dose-dependent.
- 4 The effects of pindolol 0.045 mg/kg i.v. (mean total dose 3.5 mg), pindolol 5 mg p.o., propranolol 0.3 mg/kg i.v. (mean total dose 25.1 mg) and propranolol 80 mg p.o. were assessed on resting, standing and exercise heart rates. Neither drug reduced resting heart rate but propranolol reduced standing heart rate from 98.8 to 80.3 beats/min. The effects of all four preparations on exercise heart rate were similar.
- 5 Oral pindolol is approximately 16–20 times as potent as oral propranolol.
- 6 Intravenous pindolol is approximately 6–8 times as potent as intravenous propranolol.

Introduction

Estimates of the relative potency of pindolol have varied greatly. Waal-Manning & Simpson (1974) compared the antihypertensive effects of pindolol and propranolol, employing doses of pindolol which were a quarter those of propranolol. Frishman (1980) has also utilized pindolol doses which were a quarter of the corresponding doses of propranolol. In a formal comparison of propranolol and pindolol on exercise heart rate, Aellig (1976) concluded that the maximum effects of pindolol 5 mg and propranolol 100 mg were approximately equivalent. Although Aellig (1976) concluded that there were differences in the duration of action of each drug, he estimated the relative potency twenty to one. The fivefold discrepancy in dosage ratios presents a problem for the clinician who wishes to change β -adrenoceptor blocker therapy and has important implications for the comparison of efficacy and adverse effects between studies. Inadequate or incorrect information

about the relative potency of different drugs may have important consequences for drug prescribing.

The principal objective of the following study was the resolution of the question of relative potency of oral pindolol and propranolol. Additional objectives included the comparison of the oral dose-response curve of pindolol with known dose-response relationships for other β -adrenoceptor blockers, a comparison of oral and intravenous dose-response curves of pindolol and propranolol and a re-assessment of the comparative duration of action of pindolol and propranolol. Additional objectives which will not be described at this time included the comparative bioavailability of pindolol and propranolol, the concentration-response relationships of oral and intravenous pindolol and propranolol and other pharmacokinetic comparisons of pindolol and propranolol within the same group of individuals (Carruthers, Pacha & Aellig, to be published).

Methods

Subjects were eight healthy males aged 20–29 years (mean age 25.5 years, mean weight 77.1 kg) who agreed to participate in a series of studies to evaluate the clinical pharmacology of pindolol. All subjects were healthy, without obvious risk factors for β -adrenoceptor blockers and were asked to sign written consent forms approved by the Human Experimentation Committee at the University of Western Ontario.

Subjects received drugs in a randomly assigned single-blind manner. Oral drugs were administered in the fasting state with 100 ml of water. Intravenous agents (propranolol 1 mg/ml and pindolol 0.2 mg/ml), were infused at the rate of 1 ml/min, also in the fasting state. Subjects were studied at three levels of sympathetic activity, namely resting heart rate (RHR) measured after the subjects had rested quietly in the supine position for at least 20 min, standing heart rate (SHR) measured as the maximum rate achieved on assuming the erect position without otherwise moving and exercise heart rate (EHR) after 2.5 to 3 min of vigorous exercise on a treadmill to achieve 85–90% of predicted maximum heart rate for the subject's age and sex.

Subjects received oral doses of pindolol 0.25 mg,

0.5 mg, 1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg after control observations of RHR, SHR and EHR. The three smallest doses were given in the form of specially prepared capsules (Anka Pharmaceuticals, Whitby, Ontario). The other preparations were conventional Viskin tablets, a fraction ($\frac{1}{2} \times 5$ mg tablet) or multiple tablets (2×10 mg tablets).

In a subsequent study, the effects on RHR, SHR and EHR of intravenous pindolol 0.005, 0.01, 0.02 and 0.045 mg/kg were measured. For purposes of comparison with propranolol and oral pindolol, the same subjects received pindolol 5 mg p.o., propranolol 80 mg p.o. and propranolol 0.3 mg/kg i.v.

Effects on heart rate of individual doses were assessed at 0 h (control), 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h and 24 h, unless an earlier observation demonstrated a return of exercise heart rate to within 5% of the control value. Statistical analysis was performed by analysis of variance.

Results

The effects of the three smallest doses of pindolol 0.25 mg, 0.5 mg and 1 mg are presented in Figure 1. The effects of all three doses were significantly different from control at 2 h (0.25 mg $P < 0.05$; 0.5 mg

Figure 1 Effects of oral pindolol 0.25 mg (○), 0.5 mg (●) and 1 mg (△) on resting (RHR), standing (SHR) and exercise heart rate (EHR). Mean $\pm$ s.d. results, $n = 8$.

Table 1 Relative potencies of individual β -adrenoceptor blocking drugs producing 10%, 15%, 20% and 25% reduction of standardized exercise heart rate

Drug	10%		15%		20%		25%	
	(mg)	dose-ratio	(mg)	dose-ratio	(mg)	dose-ratio	(mg)	dose-ratio
Atenolol	—	—	15.2	(21.1)	23	(14.1)	150	(9.7)
Oxprenolol	—	—	13.5	(18.8)	20	(12.5)	50	(3.2)
Pindolol	0.35	(1)	0.72	(1)	1.6	(1)	15.5	(1)
Practolol	—	—	31.5	(43.8)	61	(38.1)	250	(16.1)
Propranolol	12	(34.3)	18	(25)	32	(20)	105	(6.8)
Sotalol	34	(97.1)	115	(159.7)	220	(137.5)	255	(16.5)

The doses are also expressed as a relative ratio of the most potent drug, pindolol (1).

Note that the ratio depends on the effect at which the doses are compared.

$P < 0.05$; 1 mg $P < 0.02$). At 4 h, the smallest dose was no longer effective in reducing heart rate and at 8 h none of the doses was significantly different from control ($P < 0.05$).

The dose-response curve for all eight doses of pindolol is presented in Figure 2. The effects of pindolol have been expressed as the percentage reduction of EHR, a method of assessing β -adrenergic receptor blockade which has been validated as a measure of assessing β -adrenergic receptor blockade of cardiac chronotropic activity (Carruthers *et al.*, 1976). All observations presented are derived from the maximum observed responses at 2 h after oral dosing.

The dose-response curves of other β -adrenoceptor blockers derived in a similar manner from studies of healthy, young male volunteers undergoing sub-maximal exercise 2 h after single oral doses of β -adrenoceptor blockers were performed while the author was a trainee at the Queen's University of Belfast (Carruthers *et al.*, 1974; Carruthers, 1975; Brown *et al.*, 1976a; Brown *et al.*, 1976b; McDevitt *et al.*, 1977).

Pindolol did not reduce RHR or SHR significantly.

All doses of pindolol reduced EHR significantly. There was no significant difference between the effect produced at 2 h by 2.5 mg and the effect produced at 2 h by 20 mg. The configuration of the dose-response curve for oral pindolol differed in three respects from other β -adrenoceptor blockers: (1) potency, (2) slope and (3) efficacy. The relative potencies of the individual drugs are presented in Table 1. This table has been developed from the dose-response curves presented in Figure 2. Because it presents the greatest potency, pindolol has been designated 1 in terms of relative potency. The effective doses of the different agents which reduce exercise heart rate by 10%, 15%, 20% and 25% have been derived by interpolation. Pindolol is extremely potent compared to the other β -adrenoceptor blockers studied. At 2 h after dosing, a 10% reduction of EHR is produced with an average dose of 0.35 mg, a 15% reduction of EHR with 0.72 mg, a 20% reduction of control EHR with 1.6 mg and 25% reduction of EHR with 15.5 mg. It is apparent from Table 1 that the relative potency of the other β -adrenoceptor blockers varies according to the reduction of EHR at which the comparison is made. Over those parts of

Figure 2 Comparison of oral pindolol ($\square$) dose-response curve with historical controls who received other β -adrenoceptor blocking drugs (Δ oxprenolol, $\blacktriangle$ atenolol, $\circ$ propranolol, $\blacksquare$ practolol and $\bullet$ sotalol). For pindolol $n = 8$, for the other drugs $n = 6$.

Figure 3 Effects of (mean $\pm$ s.d.) of intravenous pindolol (Δ 0.005 mg/kg, $n=8$; $\blacktriangle$ 0.01 mg/kg, $n=8$; $\circ$ 0.02 mg/kg, $n=6$; $\square$ 0.045 mg/kg, $n=8$) on resting (RHR), standing (SHR) and exercise heart rates (EHR).

Figure 4 Comparison of the effects on exercise heart rate (EHR), standing heart rate (SHR) and resting heart rate (RHR) of oral and intravenous pindolol ($\square$ 0.045 mg/kg i.v., $\blacksquare$ 5 mg p.o.) and propranolol ($\circ$ 0.3 mg/kg i.v., $\bullet$ 80 mg p.o.). (From Carruthers (1982), with permission of the publishers.)

the dose-response curves which were approximately parallel, the relative potency of pindolol to propranolol ranged from 20:1 to 32:1.

The configuration of the dose-response curve for oral pindolol differs from the dose-response curves of propranolol, atenolol and sotalol but is similar to the dose-response curves of practolol and oxprenolol in that the slope of the linear part of the relationship between the effect and the logarithm of dose appears somewhat flatter, and the maximum effect is lower.

The effects of the intravenous doses of pindolol on heart rate are presented in Figure 3. None of the four doses studied reduced RHR or SHR significantly but all doses reduced EHR. The maximum effects of all four doses were observed at the first observation at 30 min after dosing. The magnitude and duration of response was dose-related. The effects of individual doses were significantly different from control EHR until 30 min (0.005 mg/kg), 1 h (0.01 mg/kg), 4 h (0.02 mg/kg) and 8 h (0.045 mg/kg) respectively.

The comparative effects of pindolol 0.045 mg/kg i.v., pindolol 5 mg p.o., propranolol 0.3 mg/kg i.v. and propranolol 80 mg p.o. are presented in Figure 4. Neither drug reduced RHR. Propranolol reduced average SHR significantly from 98.8 beats/min to 80.3 beats/min ($P < 0.05$). The effects of all four preparations on EHR were similar. The maximum effect of both i.v. drugs were observed at 30 min after dosing, the maximum of pindolol p.o. at 1 h and propranolol p.o. at 2 h. The relative potency of pindolol and propranolol on RHR cannot be assessed since neither drug reduced this heart rate. The relative potency of pindolol and propranolol cannot be assessed on SHR since only propranolol reduced this rate. When the effects on EHR are compared, oral pindolol is approximately sixteen times as potent as oral propranolol. Oral pindolol 5 mg produced slightly greater effects than intravenous pindolol 0.045 mg/kg (average dose 3.5 mg), suggesting that the bioavailability of oral pindolol is at least 70%. Oral propranolol 80 mg reduced EHR to an extent similar to that produced by intravenous propranolol 0.3 mg/kg (average dose 23.1 mg) suggesting that the bioavailability of oral propranolol is approximately 28%. Intravenous pindolol is approximately seven times as potent as intravenous propranolol.

At 24 h there was no significant residual effect on EHR of any of the four doses. In the period 1 h–8 h, the average rate of decline of effect of pindolol on EHR was $2.4 \text{ beats min}^{-1} \text{ h}^{-1}$, while the effect on EHR of intravenous propranolol over the same period of time declined at an average rate of $3.5 \text{ beats min}^{-1} \text{ h}^{-1}$.

Discussion

Utilizing both historical and contemporary controls

for comparison, the relative potency of oral pindolol to oral propranolol has been shown to be approximately 16 to 20:1. This supports the conclusions of Aellig (1976). The methodological problems in determining relative potency are apparent since different conclusions may result from comparison of different effects and even the comparison of the same effect at different points in the dose-response curve. Within the actual dose-response curve, a fivefold variation in relative potency is demonstrated. As the pindolol dose-response curve flattens earlier, it is irrational to make numerical comparisons near the top of the pindolol response curve and, clearly, it is as unreasonable to compare effects of propranolol doses above the pindolol maximum as it is to compare the effects of various doses of propranolol on SHR with those of pindolol doses. This problem highlights the methodological difficulty of comparing dose- or concentration-response curves which differ in configuration and maximum effects exerted.

The lower maximum responses and the apparently flatter slopes of the dose-response curves following pindolol, practolol and oxprenolol suggest that the only common ancillary property shared by these drugs, namely partial agonist activity or intrinsic sympathomimetic activity, is responsible for these configurational differences. This concept is supported by earlier studies in which the concentration-response relationships of the different agents has been evaluated (Carruthers, 1975), and in which the partial agonist activity has been measured by interaction with β -adrenoceptor blockers devoid of this property (McDevitt *et al.*, 1977; Carruthers & Twum-Barima, 1981).

In this study the duration of action of both pindolol and propranolol were shorter than reported by Aellig (1976). In both of our studies described, there was no significant residual effect on EHR of pindolol 5 mg at 24 h whereas Aellig (1976) described a residual β -adrenoceptor blockade of approximately 36% of the maximum effect demonstrated at 2 h. The subjects in all studies were healthy young males of a similar age group, but Aellig (1976) employed a bicycle ergometer whereas these studies employed a treadmill. The level of sympathetic activity may differ between these tests.

Intravenous pindolol is a potent, effective and safe β -adrenoceptor blocking drug. The comparative effects of oral and intravenous pindolol indicate that the bioavailability of oral pindolol is at least 70%, a figure which is substantially above the 53% reported by Jennings and his colleagues (1979) but were in accordance with the 87% reported by Meier & Nuesch (1977). Preliminary plasma concentration data support this conclusion.

These results support the conclusion of Aellig (1976) that the effect of pindolol on exercise heart

rate declines at a slower rate than the effect of propranolol. The elimination of half-life of pindolol (3–4 h) is somewhat longer than that of propranolol (2–3 h), which may explain the longer action of pindolol. Differences in the decline of effect may also result from differences in the slopes of dose- or concentration-response relationships (Gibaldi & Levy, 1972). Such a difference is possible between the dose-response curves of pindolol and prop-

ranolol, with pindolol demonstrating a seemingly flatter curve and propranolol an apparently steeper dose-response curve. Since this difference appears to be the result of the partial agonist activity of pindolol, it follows that the longer duration of action of pindolol compared with propranolol may also be the result of its partial agonist activity.

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