The effects of a single dose of dilevalol on [^3H]-noradrenaline plasma kinetics and plasma lipoprotein cholesterol concentrations

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- 1 A single oral dose of dilevalol (200 mg or 400 mg) or placebo was administered to 15 normal male volunteers in a double-blind, random order crossover study.
- 2 Dilevalol had no significant effect on supine blood pressures or heart rates, but caused a significant fall in systolic blood pressure 1 and 30 min following standing, and attenuated the rise in diastolic blood pressure and heart rate that accompanies standing.
- 3 Dilevalol caused a dose dependent increase in plasma noradrenaline levels from arterialized blood which was due to an increase in noradrenaline spillover with no change in clearance.
- 4 Dilevalol increased plasma levels of the noradrenaline metabolite 3,4-dihydroxy-phenylethylene glycol (DHPG) (which is formed in sympathetic nerves following neuronal uptake of noradrenaline), indicating that the increase in noradrenaline spillover was not due to the blockade of neuronal uptake.
- 5 Acute dilevalol administration had no effect on total plasma cholesterol, HDL-cholesterol or LDL-cholesterol levels.

Keywords dilevalol noradrenaline lipoproteins

Introduction

Dilevalol (SCH 19927) (the R'R' optical isomer of labetalol) is a non-selective β -adrenoceptor antagonist with potent vasodilating effects in man which are due to β_2 -adrenoceptor intrinsic sympathomimetic activity (Matsunaga *et al.*, 1985; Louis *et al.*, 1989). Intravenous dilevalol given acutely to patients with severe hypertension has been shown to increase plasma noradrenaline levels (Wallin *et al.*, 1988). Propranolol, a non-selective β -adrenoceptor blocker with no intrinsic sympathomimetic activity has also been shown to increase acutely plasma noradrenaline levels, an effect which is due to a reduction in noradrenaline clearance rather than an increase in the rate at which it is released

from sympathetic nerves and enters plasma ('spillover') (Best & Halter, 1985). It is not known whether the increase in plasma noradrenaline levels following acute dilevalol administration is due to a reduction in noradrenaline clearance or an increase in noradrenaline spillover.

Drugs which have β_2 -adrenoceptor agonist activity such as dilevalol appear to share a common property of increasing plasma high density lipoprotein cholesterol (HDL-C) levels, and thus produce favourable effects on plasma lipid profiles. The selective β_2 -adrenoceptor agonist terbutaline (Hooper *et al.*, 1981) and pindolol, a β -adrenoceptor antagonist with β_2 -

adrenoceptor intrinsic sympathomimetic activity have both been reported to increase plasma HDL-C levels (Howes & Louis, 1988). In contrast, non-selective β -adrenoceptor antagonists without intrinsic sympathomimetic activity appear to reduce plasma HDL-C levels to a greater extent than β_1 -adrenoceptor selective antagonists, further suggesting a role for β_2 -adrenoceptors in the regulation of plasma HDL-C levels (Howes & Louis, 1988). However, it is uncertain whether changes in HDL-C occur acutely following the administration of β_2 -adrenoceptor agonists or antagonists, or occur only during chronic therapy.

The present study investigated the effects of acute dilevalol administration on plasma noradrenaline levels, [3 H]-noradrenaline plasma kinetics and on plasma HDL-C levels, low density lipoprotein cholesterol (LDL-C) levels and total plasma cholesterol levels.

Methods

Study design

The study followed a double-blind crossover, random order design comparing the effects of placebo, dilevalol 200 mg and dilevalol 400 mg given orally as a capsule to 15 normal male volunteers.

The subjects attended at 08.00 h having had a standard light breakfast of two slices of toast and a glass of fruit juice at 07.00 h, and having abstained from caffeine from 24.00 h the previous evening and from alcohol for 24 h. An indwelling plastic cannula was inserted into an antecubital vein of the right arm and another was inserted into a vein on the dorsum of the left hand. The subjects then rested supine for 30 min when the test capsule (placebo, dilevalol 200 mg or dilevalol 400 mg) was administered orally with 200 ml of water. The subjects then rested supine for a further 2 h after which supine blood pressures and heart rates were recorded using a Dynamap Critikon semi-automatic recorder (average of three readings 1 min apart). An infusion of 1-ring 4,5,6-[3 H]-noradrenaline (1.1-TBq mmol $^{-1}$, New England Nuclear) was then commenced via the antecubital vein in the right arm and continued for 1 h. The purity of the [3 H]-noradrenaline was checked monthly by high performance liquid chromatography and was always greater than 96%. [3 H]-noradrenaline (2.33 MBq) was added to 55 ml of sterile 0.9% NaCl solution containing 500 mg of ascorbic acid under sterile laminar flow conditions in the Hospital's Pharmacy Department. A sterile

microfilter was placed between the syringe and the infusion line. The [3 H]-noradrenaline was infused at a constant rate (55 ml h $^{-1}$) using a Braun infusion i.v. pump. The amount of noradrenaline infused (30 pmol min $^{-1}$) was well below the threshold necessary to produce detectable physiological effects or alterations in plasma noradrenaline levels. Thirty minutes before the end of the infusion, the subject's left hand was immersed in a water bath at 42° C. This procedure leads to diversion of blood flow from the arterial to the venous systems in the hand. Venous blood sampled from the dorsum of the hand in this manner closely approximates arterial blood for a wide range of metabolic compounds including noradrenaline, and is termed arterialized blood (Best & Halter, 1985). Blood was sampled from the cannula in the dorsum of the left hand 45, 50 and 55 min following the commencement of the infusion for the determination of endogenous noradrenaline levels and [3 H]-noradrenaline specific activity.

Immediately following the infusion of [3 H]-noradrenaline, the left hand was removed from the water bath and the cannula removed from the dorsum of the hand. The subject's supine blood pressure and heart rate was then recorded (mean of three readings) and blood was taken from the antecubital vein in the right arm for plasma lipoprotein cholesterol and haematocrit estimations. The subjects then stood for 1 min when erect blood pressure and heart rate recordings were taken, and blood was taken for plasma lipoprotein cholesterol, noradrenaline and haematocrit estimations. The subjects then remained ambulant (always in the erect position) for 30 min within the Clinical Research Area, after which a further set of erect blood pressure recordings were taken and blood was sampled for plasma lipoprotein cholesterol levels, noradrenaline levels and haematocrit estimations. The remaining intravenous cannula was then removed and the subjects provided with lunch.

Plasma noradrenaline assay and [3 H]-noradrenaline kinetic estimations

Blood was collected into chilled lithium heparin tubes and placed immediately on ice. Plasma was separated immediately by centrifugation for 10 min at 1,000 g at 4° C. The samples were stored at -80° C and assayed within 4 days. 'Cold' and [3 H]-noradrenaline were extracted from the plasma using a combined cation-exchange-alumina technique using dihydroxybenzylamine as an internal standard (Howes &

Rowe, 1987). Endogenous noradrenaline and dihydroxybenzylamine were assayed in an aliquot of the final extract by high performance liquid chromatography with electrochemical detection (h.p.l.c.-ECD) (Howes *et al.*, 1983). [^3H]-noradrenaline clearance was calculated from the formula:

$$\text{Clearance} = \frac{[\text{H}^3]\text{-noradrenaline infusion rate}}{\text{Specific activity of } [\text{H}^3]\text{-noradrenaline}}$$

Noradrenaline spillover was calculated from the formula:

$$\text{Spillover} = \text{Clearance} \times \text{endogenous noradrenaline concentration (Esler *et al.*, 1979)}.$$

The values for endogenous noradrenaline, noradrenaline clearance and noradrenaline spillover from each of the three time points (45, 50 and 55 min after commencing the infusion) were averaged. The unused plasma from these samples was pooled and extracted on alumina for assay of the noradrenaline metabolite 3,4-dihydroxyphenylethylene glycol (DHPG) by h.p.l.c.-ECD using dihydroxybenzylamine as an internal standard (Howes *et al.*, 1983).

The between day coefficient of variation of the assay of noradrenaline and DHPG was less than 8%, and the limit of detection for both noradrenaline and DHPG was less than 20 pg.

Lipoprotein cholesterol assay

Total cholesterol was assayed by enzyme colorimetry using the Abbott TDX semiautomated system. HDL-C was assayed using the same system following manganese sulphate precipitation of the plasma samples. LDL-C was calculated using the Friedwald approximation;

$$\text{LDL-C} = \text{Total cholesterol} - \left(\frac{\text{TG}}{2.2} + \text{HDL-C} \right),$$

where TG = the plasma triglyceride concentration. (Plasma triglycerides were assayed using the Abbott-TDX system. No values exceeded 4.0 mmol l⁻¹, the level above which the Friedwald approximation becomes inaccurate.)

All cholesterol and triglyceride estimations were performed on the day that the subject was studied. The between day coefficients of variation for the cholesterol, HDL-C and triglyceride assay were 4.9%, 5.5% and 4.6% respectively.

Blood haematocrit was determined within 60 min of sampling using a Coulter S plus.

Statistical analysis

All values presented are the mean and s.d.

Blood pressures and heart rates (for which

two values were obtained) were analysed by two-way repeated measures analysis of variance with the within person variables being treatment and time. The remaining observations were analysed by one way repeated measures analysis of variance. Pairwise comparisons between individual groups were made using the Newman-Keuls test providing a significant *F* value for the analysis of variance was obtained. When incomplete data sets were obtained, only the subjects with values recorded for all three study days were included in the analysis.

The study protocol was reviewed and approved by the Austin Hospital Human Ethics Committee.

Results

The mean age of the subjects was 23.9 ± 3.5 years, and their mean body mass index was 23.1 ± 2.4 (normal range 19.0–24.9). None of the subjects smoked.

Six subjects were unable to remain ambulant for 30 min following the period of supine rest because of dizziness, weakness and nausea and could not have the 30 min erect blood pressures and heart rates recorded. Two of the subjects were unable to remain erect on all 3 study days, and one of the subjects could not remain erect on 2 of the study days. Therefore, there were 11 occasions on which 30 min erect blood pressures and heart rates could not be recorded. In addition, a further two subjects were unable to remain erect for the same reasons as cited above while the 30 min erect blood sample (for noradrenaline, plasma lipoprotein cholesterol levels and haematocrit) was taken. One of these subjects failed to remain erect on all 3 study days, while the other subject failed to remain erect on only one occasion. Therefore there were a total of 16 occasions when 30 min erect blood samples could not be taken. There was a similar incidence of these adverse reactions in the placebo and the two active treatment phases, suggesting that the adverse reactions were due to the study procedure rather than the treatment.

There were no significant differences in heart rate or systolic and diastolic blood pressure between groups receiving placebo or dilevalol taken during supine rest prior to administration of the test capsule.

Supine blood pressures and heart rates are summarized in Table 1. Supine systolic and diastolic blood pressures and heart rates fell significantly with time on each study day, but treatment with dilevalol had no effect.

Table 1 The acute effects of oral dilevalol administration on supine systolic and diastolic blood pressure and heart rate. While all three parameters fell significantly with time ($P < 0.005$ in each case, two-way analysis of variance) dilevalol had no significant effect. Ninety-five percent confidence intervals are given for the differences between placebo and dilevalol 400 mg

	2 h	3 h
<i>Systolic blood pressure (mm Hg)</i>		
Placebo	128 $\pm$ 9	122 $\pm$ 8
200 mg	131 $\pm$ 12	121 $\pm$ 9
400 mg	129 $\pm$ 15	120 $\pm$ 9
Confidence intervals	(-8, 10)	(-5, 9)
<i>Diastolic blood pressure (mm Hg)</i>		
Placebo	67 $\pm$ 8	65 $\pm$ 5
200 mg	69 $\pm$ 6	63 $\pm$ 5
400 mg	69 $\pm$ 8	61 $\pm$ 6
Confidence intervals	(-3, 7)	(-0.01, 8)
<i>Heart rate (beats min⁻¹)</i>		
Placebo	68 $\pm$ 9	63 $\pm$ 12
200 mg	70 $\pm$ 16	62 $\pm$ 9
400 mg	71 $\pm$ 12	61 $\pm$ 9
Confidence intervals	(-6, 12)	(-5, 9)

Systolic blood pressure 1 min and 30 min following standing was significantly lower following dilevalol than following placebo (Table 2). Similarly, diastolic blood pressures 1 and 30 min following standing were significantly lower following dilevalol than following placebo, although after 1 min only the 400 mg dose of dilevalol significantly differed from placebo when pairwise comparisons were made (Table 2). Dilevalol significantly attenuated the rise in heart rate following 30 min of standing but had no effect on erect heart rates after 1 min of standing (Table 2).

Dilevalol caused a dose dependent increase in supine plasma noradrenaline levels which was due to an increase in noradrenaline spill-over with no change in noradrenaline clearance (Figure 1). Plasma noradrenaline levels following 1 and 30 min of standing were also increased by dilevalol in a dose dependent manner (Table 3).

Supine plasma DHPG levels increased following dilevalol administration compared with placebo (placebo: 4.89 ± 1.73 nmol l⁻¹, 200 mg: 8.14 ± 4.50 , 400 mg: 7.54 ± 3.14 , $P < 0.01$), reflecting the results obtained for plasma noradrenaline.

Table 2 1 min and 30 min erect blood pressure and heart rates, and supine plasma lipoprotein cholesterol levels 3 h after the administration of dilevalol or placebo

	Placebo	Dilevalol		C.I.
		200 mg	400 mg	
1 min standing systolic BP (mm Hg)	125 $\pm$ 12	118 $\pm$ 10*	114 $\pm$ 13*	—
30 min standing systolic BP ($n = 9$)	125 $\pm$ 9	115 $\pm$ 6*	115 $\pm$ 6*	—
1 min standing diastolic BP (mm Hg)	72 $\pm$ 11	68 $\pm$ 9	64 $\pm$ 9*	—
30 min standing diastolic BP ($n = 9$)	79 $\pm$ 4	69 $\pm$ 6*	69 $\pm$ 7*	—
1 min standing heart rate (beats min ⁻¹)	78 $\pm$ 19	71 $\pm$ 12	70 $\pm$ 11	(-2, 18)
30 min standing heart rate ($n = 10$)	75 $\pm$ 1	67 $\pm$ 10*	64 $\pm$ 10*	—
Supine plasma cholesterol (mmol l ⁻¹)	3.77 $\pm$ 0.73	3.67 $\pm$ 0.71	3.66 $\pm$ 0.87	(-0.42, 0.64)
Supine plasma LDL-C (mmol l ⁻¹)	2.33 $\pm$ 0.71	2.23 $\pm$ 0.63	2.18 $\pm$ 0.74	(-0.36, 0.66)
Supine plasma HDL-C (mmol l ⁻¹)	0.95 $\pm$ 0.20	0.94 $\pm$ 0.17	0.90 $\pm$ 0.20	(-0.09, 0.19)
Supine haematocrit	41.2 $\pm$ 2.5	40.9 $\pm$ 3.0	40.9 $\pm$ 2.2	(-1.5, 2.19)

* $P < 0.05$ compared with placebo (Newman-Keuls test following a significant result from one-way repeated measures analysis of variance). C.I. = 95% confidence intervals for the difference between placebo and dilevalol 400 mg.

Figure 1 Plasma noradrenaline levels, noradrenaline spillover and noradrenaline clearance 3 h post dosing. Dilevalol caused a significant increase in plasma noradrenaline levels ($P = 0.01$) due to an increase in noradrenaline spillover ($P = 0.001$, repeated measures analysis of variance). Noradrenaline clearance did not significantly differ between treatments. (95% confidence intervals between placebo and dilevalol 400 mg = -0.14 , 0.35). * $P < 0.05$, ** $P < 0.01$ compared with placebo (Newman-Keuls test).

Dilevalol administration had no effect on total plasma cholesterol, HDL-C, LDL-C or haematocrit in neither the supine position (Table 2) nor following 1 and 30 min of standing (data not presented).

Discussion

The principal finding of this study was that acute oral dilevalol administration increased plasma noradrenaline levels by increasing the spillover of noradrenaline from sympathetic nerves into plasma. In contrast, dilevalol did not alter noradrenaline clearance. In addition, dilevalol increased plasma DHPG levels. DHPG is a metabolite of noradrenaline which is formed almost entirely within sympathetic neurones by the action of monoamine oxidase (Tarlov & Lange, 1971). Most of the rise in DHPG that follows sympathetic activation occurs because of increased formation of DHPG following neuronal reuptake of noradrenaline (Goldstein *et al.*, 1988). The elevation of DHPG levels by dilevalol in the present study indicates that the increase in noradrenaline spillover was due to increased noradrenaline release rather than blockade of neuronal uptake which would tend to reduce DHPG formation (Goldstein *et al.*, 1988). This point is of importance as neuronal uptake blocking activity has been demonstrated for racemic labetalol (Kennedy & Levy, 1975; Zschiedrich *et al.*, 1983). Dilevalol thus differs from labetalol in that labetalol appears to increase plasma noradrenaline levels during chronic therapy at least in part by reducing noradrenaline clearance (Zschiedrich *et al.*, 1983). However, it must be emphasised that the method

Table 3 Plasma noradrenaline levels in forearm venous blood from an antecubital vein following 1 and 30 min of standing commenced 3 h after dilevalol or placebo administration.

	Placebo	Dilevalol	
		200 mg	400 mg
<i>Plasma noradrenaline (nmol l⁻¹)</i>			
1 min standing (n = 15)	1.77 ± 0.67	2.57 ± 0.89*	2.69 ± 1.49*
30 min standing (n = 7)	2.72 ± 0.66	4.12 ± 2.57*	4.65 ± 1.37*

* $P < 0.05$ compared with placebo (Newman-Keuls test following a significant result for repeated measures one way analysis of variance).

used to demonstrate an effect of labetalol differed from the one used in the present study in that pharmacologically active levels of cold noradrenaline were infused rather than tracer levels of an isotope. Labetalol also increases plasma noradrenaline levels following acute administration, an effect which may in part be a reflex response to the associated fall in blood pressure (Louis *et al.*, 1978). However, data on noradrenaline spillover and clearance using steady state plasma [^3H]-noradrenaline kinetics for acute labetalol administration are also not available. Dilevalol also differs from propranolol, a non-selective β -adrenoceptor blocker without intrinsic sympathomimetic activity, which acutely elevates plasma noradrenaline levels solely by reducing noradrenaline clearance (Best & Halter, 1985; Ziegler *et al.*, 1986).

The reason for the increase in noradrenaline spillover following dilevalol is unclear from the present study. It is possible that a reduction in peripheral resistance due to potent β_2 -adrenoceptor agonist effects and weaker α_1 -adrenoceptor antagonist effects (Louis *et al.*, 1989) of the drug activated the sympathetic nervous system via baroreceptor reflexes. Certainly the vasodilators nifedipine (Kiowski *et al.*, 1983) and prazosin (Mulvihill-Wilson *et al.*, 1983) acutely lower blood pressure with an associated increase in plasma noradrenaline.

An alternate possibility is that dilevalol increased noradrenaline spillover by activating presynaptic β_2 -adrenoceptors which facilitate noradrenaline release. Indeed, infusions of the β_2 -adrenoceptor selective agonist salbutamol increase plasma noradrenaline levels in man, an effect which can be prevented by pretreatment with the non-selective β -adrenoceptor blocker propranolol (Vincent *et al.*, 1984). The authors inferred that the rise in plasma noradrenaline under these circumstances was due to activation of presynaptic β_2 -adrenoceptors which facilitate noradrenaline release, but the possibility remains that the rise in plasma noradrenaline occurred

because of baroreceptor activation induced by β_2 -adrenoceptor mediated vasodilation which was subsequently prevented by propranolol.

It should be emphasized that the present study examined the effects of an acute dose of dilevalol. Whether similar increases in noradrenaline spillover persist during chronic therapy is unknown. Several studies have reported increases in plasma noradrenaline which do not persist during chronic therapy for a variety of different vasodilator drugs (Kiowski *et al.*, 1983; Fuji *et al.*, 1988; Zschiedrich *et al.*, 1983).

Dilevalol did not significantly alter supine blood pressures or heart rates in the normal volunteers studied. However, systolic blood pressure fell significantly 1 and 30 min following standing and the rise in diastolic blood pressure and heart rate that normally accompanies standing was attenuated by dilevalol. These effects may be due to the modest α_1 -adrenoceptor blocking properties of the drug (Louis *et al.*, 1989) or β_2 -adrenoceptor agonist activity in combination with its β -adrenoceptor blocking effects. Although substantial falls in systolic blood pressure occurred following 30 min of standing in some individuals (up to 14 mm Hg), the response was very variable and diastolic blood pressures were well preserved. Postural falls in blood pressure did not therefore appear to be a significant problem in young normal volunteers following acute administration.

Acute dilevalol administration had no influence on plasma cholesterol, HDL-C or LDL-C levels in either the supine or erect position. Further studies are required to determine whether chronic dilevalol therapy significantly alters plasma lipoprotein levels.

In conclusion, acute dilevalol administration increased plasma noradrenaline levels by increasing noradrenaline spillover. However, as the immediate changes in these parameters are often quite different to those that occur during chronic therapy, it will be of importance to study these indices during chronic dilevalol therapy.

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