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A comparison of acipimox and nicotinic acid in type 2b hyperlipidaemia

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The side effect profiles and lipid lowering efficacy of nicotinic acid (1 g three times daily) and its analogue acipimox (250 mg three times daily) in type 2b hyperlipidaemia were compared in a double-blind placebo controlled study. In the nicotinic acid group ($n = 7$) at 12 weeks there were significant reductions ($P < 0.05$) with respect to placebo ($n = 9$) in total cholesterol (median and range) 6.6 mmol l^{-1} (4.8–8.4) *vs* 8.8 mmol l^{-1} (7.5–9.5), triglyceride 1.4 mmol l^{-1} (0.5–4.6) *vs* 2.8 mmol l^{-1} (1.5–9.5) and apoprotein B 88.6 mg dl^{-1} (62.1–114) *vs* 121.9 mg dl^{-1} (88.0–170.7). In contrast there was no significant alteration in lipids in the acipimox group ($n = 12$). Nicotinic acid was associated with a high incidence of side effects, principally cutaneous flushing, while acipimox was well tolerated by all patients.

Keywords acipimox nicotinic acid hyperlipidaemia

Introduction

Nicotinic acid is a potent hypolipidaemic agent which has been available for over 30 years and remains popular among lipid clinic physicians in North America (Hoeg *et al.*, 1986). The lipid lowering effect of nicotinic acid is associated with both radiological regression of atherosclerotic lesions and a reduced incidence of coronary artery disease (Brown *et al.*, 1990; Olsson *et al.*, 1990). Despite this, it remains a little used drug in the United Kingdom because of its reported incidence of frequent and troublesome side effects, principally flushing and gastrointestinal upset (Durrington, 1989).

Acipimox (4-methylpyrazinecarboxylic acid 4-oxide) is an analogue of nicotinic acid which retains the lipid lowering effects of the parent compound but which exhibits greater patient acceptability. Using the currently recommended daily treatment doses this study compared the side effect profiles and lipid lowering efficacy of nicotinic acid (1 g three times daily) and its analogue acipimox (250 mg three times daily) in type 2b hyperlipidaemia.

Methods

Patients with Frederickson type 2b hyperlipidaemia were recruited from the lipid clinic of the Royal Victoria Hospital. The major entry criteria were a serum total cholesterol concentration between 7 and 10 mmol l^{-1} and a fasting serum triglyceride > 2 mmol l^{-1}. The major exclusion criteria were: thyroid disease; diabetes mellitus; apoprotein E2/E2 phenotype, serum creatinine > 0.125 mmol l^{-1}; elevation of serum bilirubin or elevation of serum liver enzyme activity to greater than twice the upper limit of the laboratory reference interval; treatment with drugs known to interfere with lipid metabolism. All patients refrained from taking aspirin or other non-steroidal anti-inflammatory agents for at least 7 days prior to randomisation as the flushing induced by nicotinic acid and its analogues is prostaglandin mediated and may be inhibited by such drugs (Edlund *et al.*, 1990).

During a 4 week dietary run-in phase patients became established on a modified fat diet (fat intake less than 32% total calories, high polyunsaturated:saturated ratio and a daily cholesterol intake of less than 300 mg). At the end of this period patients were randomised in a double-blind fashion to receive either acipimox 250 mg three times daily, nicotinic acid 1 g three times daily or placebo for a further 12 weeks. Patients were reviewed at 4 weekly intervals and at each review blood was taken for lipid profile, full biochemistry profile, apoproteins A and B, lipoprotein(a) (Lp(a)), fibrinogen and viscosity.

The first dose of study medication was taken under supervision at the clinic and patients were observed for the development of flushing. The time of onset of flushing (if any) in relation to dosing, the duration of flushing and the time taken to reach peak flush intensity were noted. The intensity of peak flushing was graded

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on a scale of 0–6 by one observer who assessed all patients, where 0 = no flushing and 6 = bright red 'beetroot' type appearance. Patients who experienced troublesome flushing were invited to take aspirin 75 mg daily before their morning dose. At each review patients were questioned on the occurrence and severity of any flushing and on the continuing requirement for aspirin.

All patients gave written consent to participate in the study and the protocol was approved by the Ethics Committee of the Queen's University of Belfast.

Laboratory methods

Cholesterol and triglyceride were measured by enzymatic methods on a Cobas Bio centrifugal analyser (Roche) and high density lipoprotein (HDL) cholesterol was measured after manganese-heparin precipitation. Apoprotein-A1 and apoprotein-B were measured by immunoturbidimetry on a Technicon RA-500 analyser with reagents from Technicon Ltd. Lp(a) was measured by Laurell rocket immunoelectrophoresis with reagents from Pharmacia Ltd. Plasma viscosity was measured using a Coulter-Harkness viscometer. Fibrinogen was measured using reagents from Boehringer-Mannheim Ltd.

The results were analysed using non-parametric statistics; the Mann-Whitney U-test and Wilcoxon ranked pairs test were used as appropriate. Results are expressed as the median with the range.

Results

Thirty-four patients were randomised—12 patients (five females, seven males) to the acipimox group; 12 patients (five females, seven males) to the nicotinic acid group and 10 patients (four females, six males) to the placebo group. The mean age was 52.2 years (range 34–66 years) and the mean body mass index at randomisation was 25.9 kg m^{-2} (range 21.9–32.1 kg m^{-2}). There was no significant difference in age distribution, body mass index or baseline lipids between the three groups, and body mass index did not change significantly during the course of the study.

Patient tolerance

Of the 34 patients randomised, 28 completed the study. All patients in the nicotinic acid group experienced significant flushing with the first dose of medication as compared with 10 out of 12 patients in the acipimox group (Table 1). Flushing with nicotinic acid was of significantly longer duration and greater peak intensity than that associated with acipimox. Despite prophylactic aspirin therapy there were five withdrawals in the nicotinic acid group (four within 3 days and one at 8 weeks) because of intractable flushing. By the end of the study period six of the seven remaining patients were experiencing mild but regular episodes of flushing (between three and 21 episodes per week) although these were not regarded as a major inconvenience.

One patient on nicotinic acid developed a transient elevation of liver enzymes (maximum serum activity: AST 54 u l^{-1}, ALT 77 u l^{-1}, GGT 56 u l^{-1}, ALP 116 u l^{-1}). Hepatitis serology was negative. The patient remained well and treatment was not interrupted.

Table 1 Flushing occurring after first dose of study medication in patients treated with nicotinic acid and acipimox. Median with range

	Nicotinic acid	*Acipimox*
Proportion of patients experiencing flush	12/12	10/12
Time after dosing to onset of flush (min)	16.5* (10–33)	34 (20–55)
Time after dosing to peak flush intensity (min)	35 (20–56)	44 (22–95)
Peak flush intensity	4.3* (3–6)	2.3 (1–4)
Duration of flush (min)	117.5* (45–215)	70 (6–270)

* = $P < 0.05$ nicotinic acid *vs* acipimox.

In the acipimox group there was no requirement for prophylactic aspirin beyond the second day of treatment and no patients reported flushing after the third day of treatment. Acipimox was well tolerated by all patients and no other adverse events were noted.

In the placebo group, no adverse effects were recorded but one patient withdrew because of an intercurrent illness.

Lipids

Table 2 shows the results in those patients who completed the study. In the nicotinic acid group the major changes at 12 weeks were a 19.5% reduction in median cholesterol, a 52% reduction in median triglyceride and a 26% reduction in median apoprotein B concentration (all $P < 0.05$ *vs* placebo). A 40% increase in HDL and a 60% decrease in Lp(a) were not significant against placebo. There was no significant change in lipids in the acipimox or the placebo groups. Rheological indices were unchanged in all groups.

Discussion

In this study nicotinic acid proved a more effective lipid lowering agent than acipimox. Significant reductions in total cholesterol, triglycerides and apoprotein B concentrations were observed. In contrast, acipimox treatment was not associated with any significant alteration in lipids. Although previous studies have shown acipimox to be effective in types 3 and 4 hyperlipidaemia (Crepaldi *et al.*, 1988; Stuyt *et al.*, 1985) it appears to be less effective in type 2 patients (Sirtori *et al.*, 1981). Using the higher dose of 1200 mg daily a 12% reduction in cholesterol and a 20% reduction in triglyceride was observed in type 2b patients (Crepaldi *et al.*, 1988). Thus one reason for the observed lack of effect of acipimox in this study may be that the dose chosen (750 mg daily) was insufficient, although this is the currently recommended dose. In addition the

Table 2 Lipids, apoprotein concentrations and rheological indices before (B) and after 12 weeks (12 w) treatment with nicotinic acid (n= 7), acipimox (n = 12) or placebo (n = 9). Median with range

	Nicotinic acid		*Acipimox*		*Placebo*	
	B	*12 w*	*B*	*12 w*	*B*	*12 w*
Total cholesterol (mmol l^{-1})	8.2 (6.8–8.8)	6.6* (4.8–8.4)	8.8 (7.0–10.5)	8.6 (7.0–10.1)	8.7 (7.0–9.7)	8.8 (7.5–9.5)
Triglyceride (mmol l^{-1})	2.9 (2.1–6.3)	1.4* (0.5–4.6)	3.3 (2.1–5.2)	2.7 (1.4–5.8)	2.8 (2.1–4.0)	2.8 (1.5–9.5)
HDL cholesterol (mmol l^{-1})	1.2 (0.8–1.4)	1.8 (1.1–2.1)	1.3 (1.0–1.9)	1.32 (1.1–1.8)	1.4 (0.8–2.0)	1.48 (0.7–1.9)
Apoprotein A1 (mg dl^{-1})	119.6 (88.3–130.3)	134.5 (95.1–145.2)	126.2 (85.0–146.3)	113.6 (88.6–151.5)	141.3 (74.6–168.2)	134.1 (87.6–168.3)
Apoprotein B (mg dl^{-1})	120.3 (66.9–166.6)	88.6* (62.1–114)	123.7 (65.7–147.5)	117.8 (60.6–160.5)	127.9 (95.9–152.3)	121.9 (88.0–170.7)
Lipoprotein (a) (mg dl^{-1})	21.8 (5–88.2)	8.8 (5–29.4)	10.2 (5–84.3)	18.9 (5–100.4)	15.9 (5–116.5)	14.5 (5–99.0)
Viscosity (centipoise)	1.73 (1.69–1.89)	1.75 (1.57–1.98)	1.80 (1.58–1.97)	1.76 (1.62–1.89)	1.77 (1.63–1.87)	1.73 (1.62–1.97)
Fibrinogen (g l^{-1})	2.8 (2.1–2.95)	2.4 (2.1–2.8)	2.5 (1.9–3.6)	2.5 (1.78–2.8)	2.6 (2.1–3.4)	2.3 (1.66–2.7)

* $P < 0.05$ *vs* placebo.

patients studied here had only moderate hypertriglyceridaemia (median triglyceride concentration 3.3 mmol l^{-1}) whereas acipimox may have a more pronounced triglyceride lowering effect in more severe hypertriglyceridaemia (Ball *et al.*, 1986). Finally given the small numbers of patients it is difficult to exclude a type 2 statistical error.

Treatment with nicotinic acid was associated with a high incidence of side effects, principally cutaneous flushing. Prophylactic aspirin was useful for controlling flushing in the initial stage of therapy. In patients who progressed beyond this stage tolerance rapidly developed and severe flushing was not a significant problem. Thus in motivated patients given prophylactic aspirin, the well documented cutaneous side effects of nicotinic acid need not be intolerable. In addition it is customary in clinical practice to commence therapy with a low dose of nicotinic acid and build up to the full therapeutic dose. Unlike nicotonic acid acipimox was well tolerated by patients and flushing was mild. However, this dose was not associated with a significant lipid lowering effect and it is not clear whether a higher and perhaps more effective dose would be associated with more marked cutaneous side effects.

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