Clinical and laboratory responses to niceritrol in the treatment of hypercholesterolaemia

L.D. Curtis,¹ J.P.D. Reckless,² A.F. Winder³ and D.J. Betteridge¹

¹Department of Medicine, University College and Middlesex School of Medicine, University College London, ²Royal United Hospital, Bath and ³Leicester Royal Infirmary, Leicester, UK.

Summary: Twenty-five hypercholesterolaemic patients from three centres in the UK were investigated in an open study of the efficacy and side effects of niceritrol. Five patients dropped out of the study at an early stage and had insufficient data for analysis. There were 13 males and 7 females (mean age 49.2 years, range 18-69). Fourteen patients had heterozygous familial hypercholesterolaemia, and six polygenic hypercholesterolaemia. Niceritrol was started at a dose of 750 mg/day and this was increased at weekly intervals over 4 weeks to the maximum tolerated dosage up to 3 g/day. This was then maintained for a further 8 weeks. There were statistically significant decreases in total plasma cholesterol, total triglyceride, LDL cholesterol and VLDL triglyceride; HDL cholesterol remained unchanged after 12 weeks of treatment (Wilcoxon matched pairs, signed ranks test). The 14 patients with familial hypercholesterolaemia showed a 13.9% fall in total cholesterol and a 19.8% fall in LDL cholesterol. All patients reported flushing and some had gastrointestinal symptoms but 19 would have been prepared to continue with the therapy at doses up to 3 g/day. Thus niceritrol has been found to be beneficial in the treatment of both familial and polygenic hypercholesterolaemia.

Introduction

Hypercholesterolaemia is widely accepted as an independent risk factor for the development of atherosclerotic heart disease.¹ Recently reported intervention studies have suggested that cholesterol reduction may reduce vascular risk² or retard the progression of atherosclerosis.^{3,4}

The nicotinic acid derivative niceritrol (pentaerythritoltetranicotinate) has been shown to be useful in the treatment of hyperlipidaemia with possibly less side effects than the parent compound.⁵⁻⁷ The current report is of a pilot study in three centres in the UK which aimed to assess the efficacy of niceritrol in lowering blood lipids and lipoproteins and to note the incidence and severity of side effects with particular reference to flushing.

Materials and methods

Patients admitted to the study included 14 with

familial hypercholesterolaemia as diagnosed by the following criteria: total plasma cholesterol level >7.5 mmol/l or LDL cholesterol level >4.9 mmol/l, plus tendon xanthomas in the patient or a first or second degree relative. The remaining patients who had plasma cholesterol levels >7.5 mmol/l but with no evidence to support a diagnosis of a specific genetic disorder were classified as polygenic. The mean age of the 20 patients was 49 years (range 18-69): there were 13 males and 7 females. All patients had been treated with an appropriate cholesterol-lowering diet for at least 3 months prior to entry into the study.

Twenty-five patients were originally recruited for the study. Five of these were early withdrawals and were excluded from the analysis because of insufficient data. One of these patients developed a skin rash and appeared to be sensitive to the drug; another two had severe flushing and in one case diarrhoea also. Of the remaining two one simply failed follow-up and the other was discovered to have carcinoma of the breast before commencement of drug therapy.

Patients were started on a dose of 250 mg three times daily and the dose was increased at weekly intervals by the same amount to a maximum of 1 g

Correspondence: L.D. Curtis, M.A., M.R.C.P., Department of Medicine, University College and Middlesex School of Medicine, The Rayne Institute, University Street, London WC1E 6JJ, UK.

Accepted: 2 March 1988

three times daily. If they experienced side effects after an increase they remained on the previous dose for a further week. Two patients were unable to tolerate a dosage above 750 mg three times daily. All subjects remained on the maximum dose attained for a further 8 weeks.

Patients were assessed at baseline (visit 1), when the maximum dose up to 3 g/day had been attained (visit 2), when this dose had been maintained for 4 weeks (visit 3), and eight weeks (visit 4).

Six of the patients had stable ischaemic heart disease, one of whom also had asthma and another peripheral arterial disease. Two patients were hypertensive. One of the patients had had a partial ileal by-pass in 1980, which had partially but inadequately controlled his hypercholesterolaemia. Patients were admitted to the trial even if they were on other medication (including lipid lowering drugs), provided their condition was stable and dosages were not changed throughout the trial. Three were on atenolol, two on oxprenolol, and one on metoprolol. Two were taking cholestyramine (16 g/day) and another bezafibrate 200 mg thrice daily. One patient was on aspirin and another on aspirin and dipyridamole. Two were on thiazide diuretics.

Venous blood was taken after an overnight fast into bottles pre-coated with potassium ethylenediamine tetraacetate. Cholesterol measurements were made with the fully enzymatic CHOD/PAP colorimetric kit from Boehringer Mannheim (FRG) and triglycerides using the GPO/PAP enzymatic colorimetric kit from the same source. VLDL was isolated by ultracentrifugation at 100,000 g for 18 h at 16°C using an MSE superspeed 75 centrifuge. After removal of the VLDL band HDL was precipitated in the infranant by heparin/manganese chloride. LDL cholesterol was calculated as the difference between the total cholesterol and the sum of the VLDL and HDL fractions.

Bilirubin, aspartate transaminase (SGOT), alanine transaminase (SGPT), total plasma albumin, plasma creatinine, uric acid, gamma-glutamyl transferase and plasma alkaline phosphatase were measured using the Technicon SMAC-1 (Technicon, Tarrytown, NY, USA). Blood glucose was measured by a hexokinase method on the Cobas-Bio

(Roche Diagnostica, UK). A full haematological profile was performed using the Coulter Counter model S-Plus IV (Coulter Electronics Inc., FL, USA). The data were analysed by the Wilcoxon matched pairs, signed ranks test.

Results

Lipids

The total plasma cholesterol showed statistically significant falls from the baseline level of 8.56 ± 2.23 mmol/l at all subsequent visits: 7.36 ± 1.48 mmol/l, ($P < 0.01$) at visit 3; 7.26 ± 1.76 mmol/l, ($P < 0.01$) at visit 4 (Table I). The total plasma triglyceride also showed significant falls from the initial figure of 2.16 ± 1.36 mmol/l, to 1.57 ± 0.95 mmol/l, ($P < 0.01$) at visit 3 and 1.47 ± 0.87 mmol/l, ($P < 0.01$) at visit 4, Table I. Significant differences were also found in the LDL cholesterol subfraction which fell from 6.49 ± 2.27 mmol/l at visit 1 to 5.28 ± 1.58 mmol/l, ($P < 0.01$) at visit 3 and 5.22 ± 1.87 mmol/l, ($P < 0.01$) at visit 4 (Table I). The mean VLDL triglyceride level had fallen significantly at visit 3 to 0.86 ± 0.78 mmol/l, ($P < 0.01$) and 0.68 ± 0.66 mmol/l, ($P < 0.01$) at visit 4 compared to 1.30 ± 1.01 mmol/l at visit 1 (Table I). HDL cholesterol rose significantly from a baseline value of 1.25 ± 0.36 mmol/l to 1.52 ± 0.57 mmol/l, ($P < 0.01$) at visit 3 and remained elevated at 1.39 ± 0.46 at visit 4, although, this just failed to achieve statistical significance ($P = 0.055$) (Table I).

Patients with familial hypercholesterolaemia were analysed separately and at visit 4 significant decreases in total cholesterol (8.23 ± 1.12 mmol/l compared to 7.06 ± 1.27 mmol/l, $P < 0.05$), LDL cholesterol (6.22 ± 1.17 mmol/l compared to 4.97 ± 1.42 mmol/l, $P < 0.01$) and VLDL triglyceride (1.19 ± 0.98 mmol/l compared to 0.60 ± 0.65 mmol/l, $P < 0.01$) were observed. There was also a small increase in mean HDL cholesterol from 1.29 ± 0.39 mmol/l to 1.42 ± 0.51 mmol/l although this was not statistically significant (Table II).

Flushing of varying severity was experienced by all patients. However, it tended to improve once the dosage was stabilized and was reduced by taking

Table I Changes in lipoproteins during niceritrol therapy

Visit	Total cholesterol (mmol/l)	LDL cholesterol (mmol/l)	VLDL triglyceride (mmol/l)	HDL cholesterol (mmol/l)
1	$8.56 \pm 2.23(20)$	$6.49 \pm 2.27(20)$	$2.16 \pm 1.36(20)$	$1.25 \pm 0.36(20)$
3	$7.36 \pm 1.48^*(19)$	$5.28 \pm 1.56^*(19)$	$0.86 \pm 0.78^*(18)$	$1.52 \pm 0.57(19)$
4	$7.26 \pm 1.76^*(20)$	$5.22 \pm 1.87^*(19)$	$0.68 \pm 0.67^*(18)$	$1.39 \pm 0.46(20)$

Figures refer to mean $\pm$ s.d.; number of observations in parentheses; * $P < 0.01$.

Table II Changes in lipoproteins in: A – familial hypercholesterolaemia during niceritrol therapy; B – polygenic hypercholesterolaemia during niceritrol therapy

Visit	Total cholesterol (mmol/l)	LDL cholesterol (mmol/l)	VLDL triglyceride (mmol/l)	HDL cholesterol (mmol/l)
A				
1	8.23 ± 1.14(14)	6.22 ± 1.17(14)	1.19 ± 0.98(14)	1.29 ± 0.39(14)
3	7.30 ± 1.35*(13)	5.29 ± 1.47(13)	0.68 ± 0.64†(12)	1.59 ± 0.66(13)
4	7.06 ± 1.27*(14)	4.97 ± 1.42†(13)	0.60 ± 0.65†(13)	1.42 ± 0.51(14)
B				
1	9.32 ± 3.81(6)	7.11 ± 3.92(6)	1.57 ± 1.11(6)	1.15 ± 0.27(6)
3	7.48 ± 1.86*(6)	5.25 ± 1.94*(6)	1.23 ± 0.95(6)	1.38 ± 0.33*(6)
4	7.73 ± 2.67*(6)	5.76 ± 2.68(6)	0.89 ± 0.69(6)	1.34 ± 0.38(6)

Figures refer to mean ± s.d.; number of observations in parentheses; * $P < 0.05$; † $P < 0.01$.

Table III Changes in liver enzymes, glucose and uric acid during niceritrol therapy

Visit	Glucose (mmol/l)	SGOT (IU/l)	SGPT (IU/l)	Alkaline phosphatase (IU/l)	Gamma GT (IU/l)	Uric acid (μmol/l)
1	4.7 ± 0.7(20)	24 ± 5(20)	25 ± 15(17)	87 ± 23(20)	30 ± 20(20)	376 ± 80(19)
3	5.1 ± 0.8*(18)	29 ± 11*(19)	40 ± 19*(16)	98 ± 24†(19)	29 ± 24(19)	446 ± 97*(18)
4	4.8 ± 0.6(20)	26 ± 8(20)	30 ± 13(17)	94 ± 18(20)	27 ± 22(20)	436 ± 87*(20)

Figures refer to mean ± s.d.; number of observations in parentheses; * $P < 0.01$; † $P < 0.05$.

the tablets with food. Two patients who were co-incidentally also on aspirin were almost free of this symptom. The first was taking 300 mg/day and had only one episode of flushing with the first dose: the second was taking 300 mg on alternate days and had flushes on two to three occasions per week. Another two patients were told to try 150 mg/day of aspirin if the flushing proved troublesome and found it highly effective. The flush was sometimes associated with skin irritation. Six patients complained of nausea and two of vomiting. The latter tended to improve with a reduction in dosage.

Haematology and biochemistry

The mean of the initial platelet counts was $254 \pm 55 \times 10^9/l$ and this was found to be significantly lowered at all subsequent visits ($224 \pm 67 \times 10^9/l$, $P < 0.05$ at visit 3 and $224 \pm 60 \times 10^9/l$, $P < 0.01$ at visit 4). The mean corpuscular haemoglobin concentration at visit 4 (31.0 ± 1.3 g/dl) was significantly increased compared to visit 1 (30.3 ± 1.6 g/dl, $P < 0.01$). No other haematological index showed significant changes at any time in the trial.

The mean levels of SGOT and SGPT initially rose with treatment and were significantly elevated at visit 3 (29 ± 11 IU/l compared to 24 ± 5 IU/l, $P < 0.05$ and 40 ± 19 IU/l compared to 25 ± 15 IU/l,

$P < 0.01$, respectively). However these levels fell with continued treatment and the differences had lost statistical significance at visit 4 (Table III). The mean level of uric acid was significantly elevated from its baseline value of 376 ± 80 μmol/l to 446 ± 97 μmol/l at visit 3, $P < 0.01$ and 436 ± 87 μmol/l, $P < 0.01$ at visit 4 (Table III).

Discussion

Several studies have shown that niceritrol is an effective lipid lowering agent of a potency comparable to nicotinic acid but with possibly less severe side effects.⁵⁻⁷ Sigroth⁵ stated that niceritrol 'is equal in effect to nicotinic acid but produces fewer side effects'. Olson *et al.*⁶ concluded that niceritrol 'was evidently more effective than nicotinic acid in lowering the total cholesterol concentration', and found that serum uric acid levels were always higher with nicotinic acid. They also pointed out that although their study design did not allow a direct comparison as regards side effects, their patients expressed strong preferences for one or other of the two drugs, which meant that failure with one did not preclude success with the other.

The only other nicotinic acid derivative currently listed in the British National Formulary is nico-

furanose. This has been used as a vasodilator in peripheral arterial disease for many years, but there is virtually no published evidence of its efficacy in lowering cholesterol in clinical disease states.

The patient population in the current study had a high proportion of subjects with heterozygous familial hypercholesterolaemia and this is the first published report of a favourable effect using niceritrol in this group of patients, highly resistant to other therapy.

The ratio of LDL cholesterol to HDL cholesterol was decreased in the overall group from 5.2. to 3.75 and in the familial hypercholesterolaemics from 4.8 to 3.5. This may be of relevance since a recent angiographic study has found that ratios of less than 4 were associated with little or no progression of coronary lesions whereas levels above this did show significant deterioration over a 7-year period.⁴

The biochemical changes associated with nicotinic acid treatment and previously encountered with niceritrol were also noted in this study. There were

increases in SGOT, SGPT and alkaline phosphatase but these were never severe enough to warrant withdrawal of therapy. There was also an increase in the uric acid of many subjects but none developed clinical gout. The changes in platelet count and MCH were significant but small and their relevance is unclear.

The main side effect was flushing which affected all patients but this improved once the dosage regime was stabilized. This effect is known to be mediated by prostaglandins and aspirin has been found to be effective in reducing or abolishing the symptom during treatment with nicotinic acid⁸⁻¹⁰ and more recently niceritrol itself.¹¹ These studies have used between 120 mg and 300 mg of aspirin with each dose of nicotinic acid. We have found that a single dose of 150-300 mg of aspirin per day may be sufficient to alleviate this problem.

In view of its undoubted potency it would seem that niceritrol can provide a useful option in the treatment of severe hypercholesterolaemia.

References

1. Kannel, W.B., Castelli, W.D. & McNamara, P.M. Serum cholesterol lipoproteins and risk of coronary heart disease: the Framingham study. *Ann Intern Med* 1971, **74**: 1-12.
2. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984, **251**: 351-364.
3. Arntzenius, A.C., Kromhout, D., Barth, J.D. *et al.* Diet, lipoproteins, and the progression of coronary atherosclerosis: the Leiden Intervention trial. *New Engl J Med* 1985, **312**: 805-811.
4. Nikkila, E.A., Viikinkoski, P., Valle, M. & Frick, M.H. Prevention of progression of coronary atherosclerosis by treatment of hyperlipidaemia: a seven year prospective angiographic study. *Br Med J* 1984, **289**: 220-223.
5. Sigroth, K. Pentaerythritoltetranicotinate (Percyt) in the treatment of hypercholesterolaemia. *Acta Med Scand* 1968, **184**: 269-273.
6. Olsson, A.G., Orö, L. & Rössner, S. Clinical and metabolic effects of pentaerythritol tetranicotinate (Percyt®) and a comparison with plain nicotinic acid. *Atherosclerosis* 1974, **19**: 61-73.
7. Kibata, M., Ishida, M., Asano, K. *et al.* Clinical study of niceritrol on serum lipids in the treatment of hyperlipidemia. *Atherosclerosis* 1980, **37**: 333-342.
8. Wilkin, J.K., Wilkin, O., Kapp, R., Donachie, R., Chernosky, M.E. & Buckner, J. Aspirin blocks nicotinic acid-induced flushing. *Clin Pharmacol Ther* 1982, **31**: 478-482.
9. Illingworth, D.R., Phillipson, B.E., Rapp, J.H. & Connor, W.E. Colestipol plus nicotinic acid in treatment in heterozygous familial hypercholesterolaemia. *Lancet* 1981, **i**: 296-298.
10. Kane, J.P., Malloy, M.J., Tun, P. *et al.* Normalization of low density lipoprotein levels in heterozygous familial hypercholesterolaemia with a combined drug regimen. *New Engl J Med* 1981, **304**: 251-258.
11. Hamazaki, T., Hasunuma, K., Kobayashi, S., Shishido, H. & Yano, S. The effects on lipids, blood viscosity and platelet aggregation of combined use of niceritrol (Percyt) and a low dose of acetylsalicylic acid. *Atherosclerosis* 1985, **55**: 107-113.