Gemfibrozil in the treatment of resistant familial hypercholesterolaemia and type III hyperlipoproteinaemia

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Summary

The efficacy of gemfibrozil in the treatment of resistant familial hypercholesterolaemia and type III hyperlipoproteinaemia was evaluated in 26 individuals over a mean period of 16 months. In the untreated state both disorders are associated with a high frequency of coronary heart disease. In the former, gemfibrozil with a bile acid sequestrant reduced plasma cholesterol by 32%, an incremental decrease of 17% compared with sequestrant therapy alone. In type III, plasma cholesterol was reduced by 40% and plasma triglyceride by 70%, while high-density lipoprotein cholesterol increased by 45%. In none of the patients studied did clinical or biochemical side effects occur.

Introduction

Lipid-lowering drugs, like antihypertensives, are prescribed long-term for correction of asymptomatic disorders with a view to reduction of the risk of future disease. Such drugs are necessarily judged by rigorous criteria of safety, effectiveness and cost. Gemfibrozil, recently introduced for general use in the UK as a lipid-lowering agent, is a fibric acid derivative that reduces triglyceride and cholesterol levels by lowering plasma very-low-density and low-density lipoproteins (VLDL and LDL); it also increases high-density lipoprotein (HDL) cholesterol[1-3]. In a 5-year large-scale randomized placebo-controlled trial, few untoward effects were evident[4].

We have assessed the metabolic effects of gemfibrozil in two primary hyperlipidaemic states associated with a high risk of cardiovascular complications[5]. Remnant (type III) hyperlipoproteinaemia responds to other drugs of the fibric acid group[6], and we have studied its response to gemfibrozil in view of the low frequency of subjective and other untoward effects of this drug[1,4]. We have also used gemfibrozil in a two-drug regimen in the management of the common problem of resistant heterozygous familial hypercholesterolaemia, i.e. in patients in whom previous monotherapy or drug combinations together with a lipid-lowering diet had failed to achieve acceptable control of the hyperlipidaemia. We report here on our experience with the drug in 26 patients, followed for up to three years.

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Patients and methods

All patients attended the St Thomas' Hospital lipid clinic and each received gemfibrozil (600 mg twice daily) for a period of 3 to 36 months (mean 16 months). Thirteen patients with remnant hyperlipoproteinaemia (9 males, 4 females) and 13 with resistant familial hypercholesterolaemia (11 males, 2 females) were studied. In the latter group serum cholesterol levels had remained persistently above 7.8 mmol/l despite treatment with a bile acid sequestrant drug in maximal tolerated dosage (4-10 sachets per day), either singly or in combination with other drugs, for periods of 6 months to 7 years. Three familial hypercholesterolaemic patients were receiving the bile sequestrant drug colestipol, and 10 were treated with cholestyramine. Five of these were also receiving probucol 0.5 g twice daily, and 4 were treated with nicofuranose (Bradilan) 1 g three times daily in addition to their resin medication. All patients studied were taking a fat-modified lipid-lowering diet[7]. Two or more baseline measurements in familial hypercholesterolaemia were made during the previous sequestrant or two-drug therapy and lipid-lowering diet, not less than 3 months after the last change in medication or in dosage. In remnant hyperlipoproteinaemia they were made after stabilization (2-3 months) on a lipid-lowering diet. During the drug trial body weight did not change by more than ±2 kg.

The diagnosis of familial hypercholesterolaemia was based upon a serum cholesterol greater than 7.8 mmol/l, due to elevation of LDL cholesterol, the presence of tendon xanthomas in an index patient or in a first-degree relative and/or hypercholesterolaemia in 2 or more first-degree relatives. Type III hyperlipoproteinaemia was defined as the presence of serum cholesterol greater than 7.3 mmol/l and serum triglyceride greater than 3 mmol/l due to elevation of VLDL and intermediate density lipoproteins together with a molar ratio of cholesterol : triglyceride in VLDL of >0.6.

Table 1. Lipid response to gemfibrozil in type III hyperlipoproteinaemia (means±s.e. mean, mmol/l)

	Baseline	Treatment with gemfibrozil	Percentage incremental change
Cholesterol	12.6±1.0	7.5±0.5	
(n=13)	(8.0−18.2)	(4.7−10.3) ●	−40
Triglyceride	10.2±1.8	3.1±0.5	
(n=13)	(3.2−26.6)	(0.9−7.5) ■	−70
HDL cholesterol	1.1±0.1	1.6±0.2	
(n=9)	(0.5−1.7)	(1.1−2.9) ▲	+45

● P=0.0004
■ P=0.0006 } by 1-tailed paired t test
▲ P=0.009

Table 2. Familial hypercholesterolaemic patients (all values mmol/l)

	Baseline	Treatment on bile acid sequestrant alone or with additional agent (mean±s.e. mean)	With addition of gemfibrozil (mean±s.e. mean)	Percentage incremental change
Cholesterol (n=13)	11.3±0.5	9.3±0.4 (7.8–12.9)	7.7±0.6 (5.4–11.4) ●	−17
Triglyceride (n=11)	2.7±0.4	2.5±0.4 (1.1–5.3)	1.25±0.1 (0.6–1.7) ■	−50
HDL cholesterol (n=6)	1.3±0.2	1.1±0.1	1.3±0.2 (0.7–2.0) ▲	+18

● P=0.008
■ P=0.011 } by 1 tailed paired t test
▲ P=0.16

Table 3. Familial hypercholesterolaemic individuals: excluding poor-responders

	Treatment on bile acid sequestrant alone or with additional agent (mean ±s.e. mean)	With addition of gemfibrozil (mean ±s.e. mean)	Percentage incremental change
Cholesterol (n=10)	9.2±0.4	6.8±0.4 ●	−26
Triglyceride (n=8)	2.8±0.6	1.1±0.1 ■	−61
HDL cholesterol (n=4)	1.1±0.2	1.4±0.2 ▲	+27

● P=0.0001
■ P=0.005
▲ P=0.12

Laboratory methods

Cholesterol and triglyceride were measured in samples obtained without venous stasis, after an overnight 14-hour fast, employing automated enzymatic methods based on Boehringer-Mannheim and Wako (GmbH) reagents respectively, using the Cobas Bio centrifugal analyser. HDL cholesterol was determined using heparin/2M manganese precipitation[8].

Results

In patients with type III hyperlipoproteinaemia a 40% reduction in serum cholesterol, 70% reduction in triglyceride and a concomitant increase in HDL cholesterol of 45% were achieved (Table 1). Of the 13 patients with familial hypercholesterolaemia, 10 showed a marked response; 3 were refractory to this additional medication, their serum cholesterol levels remaining above 10 mmol/l. Considering all 13 patients, a 17% incremental reduction in serum cholesterol and a 50% reduction in triglyceride were observed on adding gemfibrozil to the pre-existing cholestyramine or colestipol therapy (Table 2). Excluding the 3 non-responders, a cholesterol reduction of 26% with a 61% reduction in triglycerides and a 27% increase in HDL were achieved (Table 3). In none of the 26 patients did any clinical or biochemical side effects develop.

Discussion

Gemfibrozil appears to be a satisfactory treatment for remnant (type III) hyperlipoproteinaemia. The response observed in this series of 13 patients was better than that documented for either clofibrate or nicotinic acid[9]. In familial hypercholesterolaemia, gemfibrozil showed a pronounced additive interaction with bile acid sequestrant drugs. It is interesting that a combination of gemfibrozil and sequestrant was more effective than that observed in a previous report in which cholestyramine and clofibrate were used[10]. In view of the possibility that sequestrant drugs may interfere with the absorption of fibrate derivatives, it is recommended that gemfibrozil should be administered before meals and cholestyramine or colestipol after meals.

There is strong evidence from controlled trials, considered singly[11] or together[12], that the extent of reduction of the incidence of coronary heart disease is directly related to the magnitude of serum cholesterol reduction. This is in conformity with the epidemiological relation between serum cholesterol and coronary heart disease mortality, which is evident over a wide range of serum cholesterol levels[13]. These considerations justify the goal of seeking therapeutic measures that maximize the reduction of elevated serum cholesterol levels, particularly in disorders such as familial hypercholesterolaemia and remnant hyperlipoproteinaemia (type III) that are strongly associated with atherosclerosis.

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Forthcoming events

Advanced Training Program in Biomedical Research Management
3-16 July 1988, Schaeffergården, Copenhagen
The second offering of a newly designed educational program in advanced management techniques tailored specifically to the biomedical research field, especially for persons already holding considerable responsibility for operational efforts and financial outlays and controls.
Further details from: Program Secretariat, Institute of Organization, Copenhagen School of Economics, Blågårdsgade 23B, DK-2200 Copenhagen N.

International Conference on Grief and Bereavement in Contemporary Society
12-15 July 1988 at the Queen Elizabeth II Conference Centre, London
Subjects to be covered will include: adult, child and family grief; bereavement following suicide, murder, disasters, war, famine; sudden death; bereavement care around the world; cultural responses to bereavement.
Further details from: Derek Nuttall, Director of Cruse, Cruse House, 126 Sheen Road, Richmond, Surrey TW9 7UR (Tel: 01-940 4818)

8th Annual Symposium on Fine Needle Aspiration
13-20 August 1988, Westin Hotel, Mani, Hawaii
Further details from: University of California, San Francisco, Extended Programs in Medical Education, Room 569-U, San Francisco, CA 94143, USA

6th European Congress of Digestive Endoscopy
4-11 September 1988
Congress Office: Sc Studio Congressi, via F. Ferrara 40, 00191 Rome, Italy

Course in Endoscopic Sinus Surgery
5-7 September 1988, University of Birmingham, UK
There will be an experienced international teaching faculty and the course will include lectures, TV, demonstrations and cadaver operations.
Further details from: Mr D J Brain FRCS, Birmingham Ear, Nose & Throat Hospital, Edmund Street, Birmingham B3 3HH, UK

4th British Danish Dutch Epilepsy Congress
7-10 September 1988, Heemstede, The Netherlands
Further details from: Congress Secretariat, Van Namen en Westerlaken, PO Box 1558, 6501 BN Nijmegen, The Netherlands

Recent Developments in Medical Imaging
12-16 September 1988, Assembly Rooms, Bath, UK
The Imaging Science and Technology Group of the Royal Photographic Society in collaboration with The Biological Engineering Society, The College of Radiographers and The European Association of Thermology
Further details from: Dr R P Clark, Laboratory for Aerobiology, Clinical Research Centre, Watford Road, Harrow HA1 3UJ, UK

Biomaterials Degradation - Fundamental Aspects and Related Clinical Phenomena
12-16 September 1988, Oporto, Portugal.
An intensive course held under the auspices of the Council of Europe
Further details from: M A Barbosa, Department of Metallurgy, Faculty of Engineering, Rua dos Bragas, 4099, Porto Codex, Portugal

3rd Leeds Psychopathology Symposium: The Psychopathology of Perception
29-30 September 1988
Further details from: Mrs Hilary L Helme, Department of Adult and Continuing Education, The University, Leeds LS2 9JT