The short term effects of bezafibrate on the hypertriglyceridaemia of moderate to severe uraemia

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1 Hypertriglyceridaemia, an atherogenic risk factor, is a well recognised complication of uraemia, and is present in the earliest stages of the disease.

2 Bezafibrate is an effective hypolipidaemic agent, and its effect in moderate to severe uraemia is documented in this study.

3 Significant reductions in serum triglyceride and cholesterol have been achieved after 1 month's therapy with a reduced dosage of bezafibrate. A reduction in the hyperinsulinaemia was also seen, but no change in the fractional removal rate of injected lipid emulsion (K_2) was observed.

4 An accelerated decline in some patients' renal function was observed, which was partially reversed on cessation of treatment. Reversible elevations in the serum creatinine phosphokinase were also seen, but no patient exhibited the myositis-like syndrome associated with clofibrate.

Keywords bezafibrate hypertriglyceridaemia uraemia

Introduction

Hypertriglyceridaemia is a metabolic abnormality frequently associated with chronic renal failure (Bagdade *et al.*, 1976) and it has been shown to be present even in the earliest stages of the disease (Norbeck & Carlson, 1981). It is characterised by an increase in very low density lipoproteins (VLDL) triglyceride and a decrease in high density lipoprotein, (HDL) cholesterol, the low density lipoproteins (LDL) usually being normal. High serum triglycerides (Carlson & Bottiger, 1972) and low serum HDL levels (Keys, 1980) have been shown to be risk factors for the development of ischaemic heart disease, and as cardiovascular disease is the major cause of death amongst uraemic and haemodialysis patients (Jacobs *et al.*, 1976), a causal link between the hypertriglyceridaemia and atherogenesis has been suspected.

Methods used in reducing the hypertriglyceridaemia of renal failure have included dietary modification, ingestion of activated charcoal and drug therapy. Carnitine has been used

with variable success (Lacour *et al.*, 1980). Clofibrate has also been employed, but its use has met with disfavour due to a high proportion of patients developing muscle damage (Pierides *et al.*, 1975; Langer & Levy, 1968), characterised by myalgia and elevated levels of creatine phosphokinase, which return to normal with cessation of treatment. The aim of the present study was to assess the efficacy of bezafibrate-2-(*P*-(2-chlorobenzamido)ethyl)phenoxy)-2-ethyl propionic acid, (Boehringer Mannheim Ltd) a clofibrate analogue whose formula is shown in Figure 1. It has been demonstrated that bezafibrate will reduce high levels of serum lipids and is well tolerated by patients in other hyperlipidaemic states (Mordasini *et al.*, 1981; Olsson, 1979; Holler *et al.*, 1979).

Methods

Nine patients, four female and five male, with

Figure 1 The formulae for a) bezafibrate and b) clofibrate.

chronic renal failure were studied. No patient was nephrotic at the time of study. The clinical details are shown in Table 1. Renal insufficiency had been documented for at least 2 years, and the range of serum creatinine was 247 $\mu\text{mol/l}$ to 825 $\mu\text{mol/l}$. Patients 1, 5 and 9 were receiving a diet of 40 g protein/day, and the dietary characteristics obtained by dietetic assessment of week 1 of the trial are shown in Table 2 and all patients were within 10% of their desired body weight (Statistics Bulletin Metropolitan Life Insurance Company, 1959). No patient had evidence of thyroid or liver disease and none suffered with diabetes mellitus or received hormonal treatment. The study

was approved by the ethical committee of the Leicester Area Health Authority.

After an overnight fast, blood was obtained for the measurement of serum lipids and insulin. Total serum cholesterol was determined by enzymatic methods (Cholesterol C System, Boehringer Mannheim Ltd) (Stahler *et al.*, 1977). HDL cholesterol was determined in the supernatant of serum using a similar method, after precipitation of other lipid fractions using phosphotungstic acid and magnesium ions (Burstein *et al.*, 1970). Serum triglycerides were determined by an enzymatic colorimetric assay (Peridochrom®, Boehringer Mannheim Ltd). Serum LDL were calculated by application of the Friedewald formula (Friedewald *et al.*, 1972). Basal serum immunoreactive insulin concentrations were determined by a specific radioimmunoassay (Becton-Dickens Ltd), and fasting blood glucose determined by the glucose oxidase method. Liver function, renal function and creatine phosphokinase were determined by standard laboratory techniques using a S.M.A.C. analyser® (Technicon Ltd).

Table 1 Clinical details of uraemic patients studied with bezafibrate

Patient	Sex	Age (years)	Serum creatinine ($\mu\text{mol/l}$)	Diagnosis	Treatment
1	F	43	674	GN	Frusemide Propranolol Aludrox Quinine
2	M	33	247	CP	Endrallazine Atenolol Bendrofluazide
3	M	37	835	GN	Atenolol Prazosin Allopurinol
4	M	48	382	HT	Atenolol Prazosin Bendrofluazide
5	F	55	582	CP	Bendrofluazide Aludrox
6	F	57	597	CP	Atenolol Frusemide Allopurinol
7	M	32	427	CP	Atenolol Prazosin Bendrofluazide
8	F	61	378	CP	Propranolol Hydrallazine Bendrofluazide Aludrox
9	M	64	524	HT	Atenolol Minoxidil Frusemide

GN glomerulonephritis, CP chronic pyelonephritis, HT hypertensive nephropathy

Table 2 Dietary profiles of uraemic patients treated with bezafibrate

Patient	Weight (kg)	Protein (g)	Carbohydrate (g)	Carbohydrate (% of total energy)	Fat (g)	Total k cals/day
1	58.0	33.7	216.7	50.0	76.3	1648
2	88.0	95.1	218.0	33.7	124.1	2429
3	78.0	66.9	189.2	45.0	63.8	1583
4	88.0	66.8	210.0	45.4	84.2	1926
5	68.0	38.2	200.0	50.3	63.4	1488
6	56.0	Not available				
7	76.0	66.0	177.0	34.0	114	1954
8	68.0	71.2	168.0	39.0	78.7	1623
9	65.0	33.8	187.0	52.0	57.5	1353

by standard laboratory techniques using a S.M.A.C. analyser® (Technicon Ltd).

An intravenous fat tolerance test was then performed by bolus injection of 20% Intralipid® (0.5 ml/kg body weight) and blood samples taken in E.D.T.A. containers at 5 min intervals for 40 min, then at 50, 60, 75 and 90 min for nephelometric measurement of the injected lipid emulsion (Lewis *et al.*, 1972). The fasting serum sample served as a blank. The fractional removal rate of Intralipid®, K_2 (%/min) was then calculated.

The patients were then instructed to take bezafibrate 200 mg/day, and after 1 week's treatment, by which time the steady state concentration had been attained, blood was obtained at 1, 2 and 24 h post ingestion and the serum deep frozen. Serum levels of bezafibrate were determined by the manufacturer (Boehringer Mannheim Ltd, Germany) using a gas chromatography method (Endele, 1979) and the average steady state serum level calculated. The reduced dose of bezafibrate was chosen, as it has been shown that the drug half-life is prolonged in renal insufficiency (Anderson & Norbeck, 1981).

After 4 weeks' treatment, blood samples were again obtained after an overnight fast, for determination of serum lipids, insulin, glucose, renal function, liver function, creatine phosphokinase, and the intravenous fat tolerance test repeated. Renal function was again determined after a further period of 2 months.

All medications and diet were kept constant throughout the study period. Any change in patients' renal function was determined by a plot of the reciprocal creatinine concentration (Mitch *et al.*, 1976).

Statistics

Spearman's rank correlation coefficient and Wilcoxon's rank sum test for paired observations, were employed.

Results

During the study period, the fasting triglyceride (TG) and cholesterol levels both decreased significantly; the median decrease in TG being 43% ($P < 0.01$) and in cholesterol 13% ($P < 0.05$). The individual values for serum lipids, insulin, glucose, K_2 and drug levels are given in Table 3. There was a tendency for the LDL cholesterol to fall, but this did not reach significance, and no change was found in HDL cholesterol levels. Fasting serum immunoreactive insulin concentrations also fell, the median by 43% ($P < 0.01$), however, no change was found in the K_2 values, and no correlation between the change in immunoreactive insulin and either K_2 , TG or blood glucose levels was noted (Table 4).

Significant elevations in serum creatinine were noted during the trial period ($P < 0.01$) and this was not completely reversed at 2 months after stopping the drug. However, in only two patients (1 and 5) did the serum creatinine during treatment differ significantly from the previously noted downward trend of the reciprocal creatinine plot. The blood urea also increased significantly during the trial period ($P < 0.01$) but had reverted to pre-treatment levels 2 months after stopping the drug (Table 5).

A significant rise in the median level of serum creatine phosphokinase (CPK) ($P < 0.01$) was found during treatment. In three patients there were marked elevations (No. 1, 39 to 475 i.u./l, No. 5, 128 to 1118 i.u./l, and No. 6, 65 to 342 i.u./l, normal range 25 to 200 i.u./l) however, in only one patient (No. 1) were any symptoms noted, which were an increase in frequency of previously present leg cramps.

Values obtained for bezafibrate concentrations show wide variation, as did the average steady state concentration (C_{ss}) (Table 3). The rise in CPK levels and the C_{ss} showed a significant positive correlation ($r = +0.766$, P

Table 3 Serum lipid, insulin and drug values for the individual patients and treatment (a = pretreatment, b = treatment)

Patient		Serum cholesterol (mmol/l)	TG (mmol/l)	HDL (mmol/l)	LDL (mmol/l)	Insulin (i.u./ml)	Bezafibrate ($\mu\text{g/ml}$)		
							C _{ss}	Peak	Trough
1	a	7.80	1.66	1.14	5.91	20.0	12.25	18.0	6.5
	b	4.10	0.94	1.44	2.24	13.0			
2	a	5.00	1.50	0.96	3.36	23.0	2.70	5.4	0.1
	b	4.35	1.27	0.99	2.79	11.0			
3	a	4.90	4.00	0.54	2.55	41.0	5.90	8.0	3.8
	b	3.40	2.14	0.71	1.72	9.0			
4	a	5.20	2.36	1.82	2.31	21.5	6.75	11.2	2.3
	b	5.07	1.32	1.18	3.29	19.0			
5	a	4.50	1.95	0.89	2.73	18.0	12.05	18.0	6.1
	b	4.10	1.42	0.86	2.60	14.0			
6	a	5.40	2.20	0.91	3.49	14.0	13.10	20.7	5.5
	b	3.85	1.02	0.88	2.51	11.0			
7	a	6.62	5.71	0.63	3.41	6.8		Not available	
	b	6.67	2.89	0.73	4.64	6.0			
8	a	5.47	2.02	0.82	3.73	20.0	10.15	15.5	4.5
	b	4.04	1.20	0.86	2.63	10.5			
9	a	5.04	1.42	0.71	3.68	18.0		Not available	
	b	5.62	1.64	0.71	4.16	18.0			

TG serum triglyceride, HDL high density lipoprotein, LDL low density lipoprotein

< 0.05), however, only when the C_{ss} exceeded 12 $\mu\text{g/ml}$ did values for the CPK lie outside the normal range. Those patients with the higher serum creatinine values tended towards a higher C_{ss}, but this did not reach significance, neither did the relationship between the decrease in lipid fractions or insulin and the C_{ss}.

There was no change in blood glucose or K₂ values (Table 4), and no significant change

in serum alanine transaminase (median 16 to 27 i.u./l), hydroxybutyrate dehydrogenase (median 194 to 270 i.u./l), haemoglobin or white cell count were noted during the study period.

During the trial period one patient (9) complained of nausea and vomiting after 3.5 weeks' treatment and endoscopically proven gastric erosions were found. This responded to cessa-

Table 4 Serum lipid, insulin K₂ and CPK values before and after treatment

	Pre-treatment		Median	Treatment Range	P
	Median	Range			
Cholesterol (mmol/l)	5.20	4.50–7.80	4.10	3.40–6.67	< 0.05
Triglyceride (mmol/l)	2.02	1.42–5.71	1.32	0.94–2.82	< 0.01
HDL (mmol/l)	0.89	0.54–1.82	0.86	0.71–1.44	NS
LDL (mmol/l)	3.41	2.31–5.91	2.63	1.72–4.64	NS
Glucose (mmol/l)	5.3	4.6–6.4	5.1	4.1–5.9	NS
K ₂ (%/min)	2.61	1.65–3.07	2.84	1.74–3.34	NS
Insulin (i.u./ml)	20.0	6.8–41.0	11.0	6.0–19.0	< 0.01
CPK (i.u./l)	73	39–211	136	59–1118	< 0.01
% Δ_{TG}			–43%	+14–53.6	
% Δ_{CHOL}			–13%	+11.5–47.4	

NS not significant

CPK creatinine phosphokinase

% Δ_{TG} percentage change in TG, % Δ_{CHOL} percentage change in cholesterol

tion of bezafibrate, and treatment with cimetidine. The other patients tolerated the treatment without ill effects.

Discussion

This study shows that serum TG and cholesterol levels have been reduced by bezafibrate after 4 weeks' treatment in patients with advanced renal failure by a similar magnitude to that seen in essential hyperlipoproteinaemia (Olsson, 1979). However, in this study no significant rise in HDL cholesterol could be demonstrated. This may be related to the short duration of the study, as HDL cholesterol levels continue to rise for up to 6 months after the initiation of treatment with bezafibrate (Moutafis, 1982).

It is thought that the hypertriglyceridaemia of uraemia is due to a decreased peripheral removal of TG, as reduced activities of lipoprotein lipase (Kraemer *et al.*, 1982) and hepatic triglyceride lipase (Mordasini *et al.*, 1977) have been found, reflecting the low fractional removal rates for injected lipid emulsions (K_2). However, an alternative postulate is an increase in the hepatic production of TG associated with the hyperinsulinaemia (Chan *et al.*, 1982). In non-uraemic hyperlipidaemic patients, bezafibrate has been shown to increase K_2 values and lipoprotein lipase activity (Vessby *et al.*, 1980) however, in this group of uraemic patients no change in K_2 values was documented, thereby raising the possibility that the major mode of action in these patients may be a reduction in hepatic TG secretion. This is supported by the significant fall in serum insulin levels. Lowering TG levels in obese patients by weight reduction, in whom a state of peripheral insulin resistance also exists (Kolterman *et al.*, 1980) will produce a reduction in insulin secretion, insulin resistance and hepatic TG secretion. This form of hypertriglyceridaemia has been postulated to be a direct result of hyperinsulinaemia (Olefsky *et al.*, 1974). A similar mechanism may be operating in uraemia, as the lack of change in the K_2 values reflects that the peripheral disposal of TG is unchanged after bezafibrate treatment. A similar finding that bezafibrate will reduce hypertriglyceridaemia but not affect K_2 values, has been found in patients with moderate renal failure treated in this way (Norbeck & Anderson, 1982).

During the study period, increases in both blood urea and serum creatinine were found. The rise in urea was reversed by 2 months after cessation of treatment, and in only two patients

Table 5 Renal function, before, during and 2 months after treatment

	Pre-treatment (A)		After 4 weeks treatment (B)		2 months post-treatment (C)		P value A vs B	P value A vs C
	Median	Range	Median	Range	Median	Range		
Urea (mmol/l)	22.5	10.3–39.6	31.2	13.1–61.7	22.3	11.3–45.2	< 0.01	NS
Creatinine (μ mol/l)	524	247–825	614	252–1105	560	233–1000	< 0.01	< 0.05

did the increase in creatinine exceed the value predicted from the reciprocal creatinine plot and on cessation of treatment the previously predicted decline in renal function was resumed. Both of these patients sustained an average steady state concentration of bezafibrate in excess of 12 µg/ml, and this high drug level and accelerated decline in renal function may be causally linked. However patient No. 6 who exhibited the highest drug level showed no such accelerated decline. Previous recommended values for the C_{ss} have been 3 to 4 µg/ml (Anderson & Norbeck, 1981) and even with the reduced dosage employed in this study drug levels far in excess of this recommended level were attained.

Significant increases in serum CPK values were seen, and those patients who sustained the higher drug levels experienced the greatest changes in CPK levels; however these too were

reversed by cessation of treatment. Those patients who experienced a decline in renal function not previously predicted (No. 1 and 5), also sustained the higher drug levels and higher CPK levels. This may be due to a nephrotoxic effect at the high levels sustained, or linked to a mild degree of muscle damage, however, no patient exhibited the myositis-like syndrome associated with clofibrate toxicity.

In summary, bezafibrate will lower TG levels in uraemic patients, however, the accelerated decline in renal function seen in some patients must question its use in advanced uraemia, unless the dosage is significantly reduced below that used in this study, so that drug levels are maintained at the level previously recommended. Also further evaluation of the exact mechanism of lipid reduction in uraemia is needed.

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