IMPROVEMENT OF HYPERLIPIDAEMIA BY BEZAFIBRATE TREATMENT IN RDT PATIENTS

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Summary

The pharmacokinetics and therapeutic effects of bezafibrate were studied in 15 RDT patients in a placebo controlled trial. Serum half life of bezafibrate was prolonged to 17 – 21.5 hours compared to 1.6 – 2.1 hours in normals. Adequate dosage in RDT patients was found to be 200mg every 3rd day. Bezafibrate treatment resulted in a significant decrease in the serum concentrations of triglycerides, total cholesterol and LDL-cholesterol, whereas HDL-cholesterol serum levels increased. Under this dosage regimen no adverse side effects were observed. Bezafibrate offers the possibility of correcting disturbances of lipid metabolism of RDT patients, possibly involved in the pathogenesis of atherosclerosis of these patients.

Introduction

About 40% of all RDT patients die from cardiovascular complications resulting from accelerated atherosclerosis [1,2]. The only proven risk factor for atherosclerosis in RDT patients is hypertension, whereas factors like impaired glucose tolerance, hyperparathyroidism and hyperlipidaemia, which are also frequently found in RDT patients, are still discussed controversially [3].

The predominant form of hyperlipidaemia in RDT patients is type IV, characterised by increased concentrations of triglycerides and VLDL. Although cholesterol levels in uraemics are in general normal, a decreased HDL cholesterol is typical [4]. Since this constellation of hyperlipidaemia coincides in non-uraemics with accelerated atherosclerosis [5], it was the aim of this study to investigate the effect of bezafibrate (BF), a recently developed lipid lowering drug, in RDT patients. The pharmacokinetics of BF were tested, its lipid-lowering effect was measured and special attention was paid to possible side effects.
Patients and methods

The study was performed in 15 patients (12m, 3f), on RDT for a mean of 4.1 years (1–8 years). Mean age was 52 years (39–61 years). From Metropolitan Life Insurance tables we calculated a normal mean body weight index of 1.09. Selection criteria were: triglycerides and/or total cholesterol concentrations higher than 300mg/dl, normal serum albumin concentration and normal standard liver enzymes.

The study was designed in an ABA-fashion, starting with a 6 weeks placebo period, followed by 12 weeks of treatment with BF in a dosage of 200mg every 3rd day. A second 6 weeks placebo period concluded the study. The following parameters were measured: fasting serum triglycerides and total cholesterol (every 2 weeks), HDL- and LDL-cholesterol at start and end of each period, and monthly during the treatment phase.

Triglycerides were measured enzymatically, total cholesterol by the CHOD-PAP method. HDL- and LDL-cholesterol were calculated from agarose lipid electrophoresis with polyanion precipitation [6]. Serum BF concentrations, measured by gas chromatography, were followed over a 72 hour period after an oral dose of 200mg at start and end of the treatment period.

Creatine phosphokinase (CK) was measured every 2 weeks, liver enzymes, haemoglobin, bilirubin and albumin monthly.

Results are presented as median values and analysed with Wilcoxon’s test.

Results

BF treatment resulted in a significant reduction of initially highly elevated triglyceride levels, which increased again after withdrawal of treatment. However, in none of the patients did triglyceride levels reach the normal range (<200mg/dl) during treatment (Figure 1). A significant decrease of total cholesterol (normal range <260mg/dl), was observed during BF treatment. Starting values were reached again during the second placebo treatment (Figure 2). The initially very low HDL-cholesterol concentrations (Figure 3) showed a marked increase of 73% under BF treatment, but only an insignificant decline during the following placebo period. In six of the patients LDL-cholesterol concentrations were elevated, but remained above the upper limit of normal (<190mg/dl) during BF treatment in only one patient. The median value after drug withdrawal did not change, however the individual response was irregular. LDL/HDL ratios dropped significantly under BF treatment and remained low for at least 6 weeks, when treatment was stopped. The 72 hour serum profiles of BF after the first and last BF administration of the treatment period were analysed. The elimination half lives, calculated from the slopes, were not significantly different (17.1 hrs for the first, 21.5 hrs for the last drug intake), but were markedly prolonged in contrast to 1.6 – 2.1 hrs in healthy subjects [7].

A minor and statistically insignificant tendency for drug accumulation could be detected after 12 weeks of treatment. The mean serum concentration of BF between 2 doses, calculated from the area under the curves, were 2.4mg/L at start and 3.4mg/L after 3 months of treatment. Both values were within the
optimal therapeutic range (median 3.0mg/L), recommended for patients without renal disease [7].

Drug side effects known to be associated with BF or chemically related substances, such as gastrointestinal symptoms, allergic skin reactions and myositis were not observed. CK increased significantly under treatment and decreased almost to the initial values afterwards, however the treatment value was still within the normal range (Table I). SGOT did not change throughout the study, whereas the other liver enzymes (SGPT, gamma-GT and AP) decreased during treatment and returned to initial values after drug withdrawal.
Discussion

The specific constellation of hyperlipidaemia found in uraemics is a proven risk factor for accelerated arteriosclerosis in patients with normal renal function [5]. Since death from cardiovascular complications is very common in dialysis patients, it seems logical to treat hyperlipidaemia in these patients, although a beneficial effect of lipid lowering treatment in uraemics is not yet established.

For a large proportion of uraemic patients correction of hyperlipidaemia by physical exercise or dietary means, because of lack of patients' compliance, will not be successful. Here use of lipid lowering drugs appears to be indicated. The use of clofibrate in RDT patients is limited, because severe side effects such as
Figure 3. Effect of bezafibrate on HDL- and LDL-cholesterol levels in regular haemodialysis patients
(n=13, ■ = median value)

myositis — probably due to a narrow therapeutic range and drug accumulation — were reported [8].

In our patients using bezafibrate in a reduced dose for the treatment of their hyperlipidaemia we saw a striking improvement of the disorders of lipid metabolism. At the same time no side effects could be observed. Probably the most important effect of bezafibrate is the pronounced increase of initially decreased HDL-cholesterol, which has been proven to be a factor protecting against the risk of coronary heart disease [5]. Further trials to investigate the long term effect of
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Mean ± SD; *p<0.05 (paired t-test)

bezafibrate on hyperlipidaemia and the incidence of cardiovascular disease in RDT patients are indicated.

References

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Open Discussion

DRÜEKE (Paris) We have previously reported that clofibrate in uraemic serum is present in a much higher free concentration than in normal serum. Have you been able to determine the free fraction of bezafibrate in uraemic serum?

GRUTZMACHER No, we haven’t determined that. We have purposely chosen patients with normal serum albumin. Maybe, as with clofibrate, hypoalbuminaemia contributes to the toxic effects of bezafibrate.

DRÜEKE Yes, but this increase was also seen in the absence of any decrease of serum albumin, so I think there might be some toxic factor in uraemic serum which is increasing the free fraction of the drug. What mechanism do you propose
for this decrease in triglycerides and the increase in HDL cholesterol? Have you had the occasion to measure, for instance, post-heparin lipolytic activity?

GRUTZMACHER No, we haven’t measured that, but it’s well investigated in normal subjects. The mechanism can be explained by an activation of both hepatic and extra-hepatic lipoprotein lipase as well as by an improvement of glucose tolerance, which may also contribute to glyceride changes.

VLAHO (Cologne) We have treated our patients with bezafibrate, too. Some patients do not respond to bezafibrate. These patients have lower HDL and higher LDL cholesterol. Have you any explanation for this?

GRUTZMACHER No. In our subjects there were also two patients who didn’t respond. The reason is unclear.