DRUG TREATMENT OF HYPERTRIGLYCERIDAEMIA IN CHRONIC URAEMIC PATIENTS: PRELIMINARY REPORT ON D,L-CARNITINE AND THIADENOL

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Summary

Clofibrate (a very effective lipid-lowering drug) may cause serious muscular damage in uraemic patients, even if used at appropriately low dose. Some authors have reported that D,L-Carnitine and Thiadenol can reduce lipid levels in non uraemic subjects, without adverse effects.

In our study D,L-Carnitine and Thiadenol were administered for 3 months to respectively 21 and 15 patients on chronic haemodialysis with hypertriglyceridaemia.

With D,L-Carnitine 52% of patients showed lower plasma triglycerides (TG) (-40.6%, p < 0.002); after Thiadenol 66.6% of patients showed reduced plasma TG concentration (-42.9%, p < 0.001). No dietary changes were recorded during the study. No major side effects nor biochemical changes were observed.

D,L-Carnitine and Thiadenol appear to be less effective, but also less dangerous than Clofibrate in chronic uraemic patients.

Introduction

A number of risk factors for atherosclerosis and coronary heart disease occur in patients on chronic maintenance dialysis. These are mainly hypertriglyceridaemia, smoking and hypertension, which persists after starting dialysis. The interaction of these risk factors might account for the marked increase in myocardial infarctions seen in this population [1–3].

Two therapeutic approaches have been tried in an attempt to lower serum lipid levels: diet modification has been reported to be successful [4], and positive results have been observed using Clofibrate low doses [5]. However most patients do not tolerate rigid dietary restrictions, whilst Clofibrate must be used with caution.

Recently two substances have been reported as lipid-lowering drugs: they are D,L-Carnitine [6], and Thiadenol [7].
This paper reports preliminary results of therapy with these drugs in patients on regular haemodialysis.

Methods

Forty-one patients on chronic maintenance haemodialysis were selected for study; the patients had been on dialysis for an average of 49 months (range 5-159 months) and performed haemodialysis 4 hours three times a week with glucose-free dialysis fluid. Patients who were examined for this study had type IV hypertriglyceridemia, with a fasting serum TG level above the 95th percentile for age and sex of a normal population [8]. No subject was diabetic or obese, or had suffered from nephrotic syndrome. Patients were not receiving androgens nor blood transfusions during the study. They took only aluminium hydroxide, iron, hydroxy-soluble vitamins and vitamin D. Diets were not prescribed except for fluids and potassium. Every month total calories, proteins, fats and carbohydrates were checked. Patients received about 38 Cal/Kg of body weight (kg/BW), 1.6g/kg/BW of animal proteins, 4.3g/kg/BW of carbohydrates, 1.5g/kg/BW of fats (half of these were poly-un-saturated fats).

No important variations in diet habits were recorded during the study.

Patients were randomly divided into two groups: 21 subjects were treated for a 3 months period with D,L-Carnitine (3 to 4g/day according to the BW, orally); 20 subjects with Thia-denol (1.6g/day orally) for three months. The two groups were not statistically different for the following variables: age (mean ± SD: 41 ± 11 years); body weight (52.6 ± 8.1kg); sex; dialytic age (49 ± 22 months); initial level of TG (315 ± 83mg/dl).

Before, during and after the study the following parameters were examined by standard methods: serum urea, creatinine, uric acid, SGOT, SGPT, CPK, alkaline phosphatase, serum electrophoresis, cholesterol, triglycerides, electrolytes, Hb and complete blood count.

Five patients have stopped the treatment with Thia-denol owing to the incidence of side effects.

Student’s ‘t’ test for paired and unpaired data and the ‘chi square’ test were applied, and the correlation factor ‘r’ and its significance estimated.

Results

With both drugs a number of patients did not show serum lipid variations (see Figures).

With D,L-Carnitine 11 patients (52%) showed a reduced mean TG concentration (184 ± 41mg/dl; - 40.6%; p < 0.002). No variations in the other biochemical parameters were observed; no side effects were demonstrated. We have only observed a rising trend in the drug weight of the patients.

Of the 15 patients who have completed the treatment with Thia-denol, 10 (66.6%) have shown mean triglycerides levels lower than 42.9% (181 ± 59mg/dl; p < 0.001). Neither in this group have variations in other biochemical parameters been noted.
Figure 1.

Figure 2.
Side effects

One subject has shown skin rash, another patient has exhibited diarrhoea; 2 patients developed nausea and another subject developed gastric pyrosis. All troubles stopped after drug withdrawal.

Responsiveness to treatment has not shown any statistically significant correlation with age, sex, body weight, dialytic age, initial level of TG.

Discussion

Clofibrate is an effective drug for lowering plasma TG levels in uraemic subjects [5]; some authors however suggest caution in its use because of potential muscle toxicity in patients on haemodialysis [9], and increase in incidence of gall stones and of neoplasia [10].

Dietary manipulation can improve lipid abnormalities; many patients however do not adhere to these [4]; besides, rigid diet restrictions must be prescribed cautiously to avoid uraemic malnutrition.

Carnitine (β-hydroxy-γ-trimethyl-ammonium-butyrate) is an essential compound in transport of free fatty acids into the mitochondria where they are oxidised. Some authors have observed carnitine deficiency induced during haemodialysis [11]; others have observed an inverse correlation between muscle and serum levels of carnitine and TG; they have also documented a decrease in TG levels with carnitine administration in healthy subjects [6]. Other authors [12] demonstrated the same effect in uraemic patients.

Our study indicates that this drug is effective in some of the treated patients, and that it is well tolerated. We have observed a trend of increase in dry weight of patients; this fact might be explained by the improved appetite reported by all patients.

Thiadenol (bis(hydroxy-ethyl-thio)1,10 decane) is effective in control of different lipid abnormalities in non uraemic patients [7]; it seems to act similarly to clofibrate, but it appears less toxic [13,14].

In our study we have noted lower triglyceride levels only in some patients; however, as Rouffy [15] has obtained the best results after 43 months of treatment, prolonging treatment may lead to more successful results. Drug tolerance was quite good, side effects were quickly reversible and not dangerous.

Though it remains to be demonstrated that a reduction in serum lipid levels in patients on haemodialysis produces a decrease in atherosclerotic complications, lipid lowering treatment seems to be indicated. Therefore we consider that D,L-carnitine and Thiadenol are noteworthy drugs, though they are less effective than clofibrate. Certainly the action of these drugs and the reason for failures require further investigations.

References

1 Lindner A, Churra B, Sherrard DJ, Scribner BH. New Engl J Med 1974;290:697
2 Bagdade JD, Cassaretto A, Albers JJ. J Lab Clin Med 1976; 87:37
3 Halre H, Sherrard DJ, Scardapane D, Bronzelli JD. Cardiovasc Med 1978; 3:1163
4 Gokal R, Mann JI, Oliver DO, Ledingham JGG. *Amer J Clin Nutr* 1978; 31: 1915
5 Sherrard DJ, Golberg AB, Haas LB, Brunzell JD. *Nephron* 1980; 25: 219
7 Rouffy J, Loeper J. *Therapie* 1972; 27: 433
8 Brunzell JD, Albers JJ, Haas LB, Golberg AP, Agadoa L, Sherrard DJ. *Metabolism* 1977; 36: 903
13 Martin E, Feldmann G. *Pathol Biol* 1974; 2211: 179
15 Rouffy J. *Therapie* 1975; 30: 815