

Effects of Gemfibrozil (Lopid®) on Hyperlipidemia in Acitretin-treated Patients

Results of a Double-blind Cross-over Study

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Hyperlipidemia is a common side-effect of oral retinoid treatment, which sometimes interferes with long-term therapy. To evaluate the safety and efficacy of the lipid-lowering drug gemfibrozil on retinoid-associated hyperlipidemia, we studied the clinical response and the plasma lipoprotein levels in 22 acitretin-treated (0.25–0.75 mg/kg) patients mainly suffering from psoriasis. Gemfibrozil or placebo was given in a double-blind cross-over fashion to 14 patients, who after 8 weeks of acitretin therapy and dietary advice exhibited hyperlipidemia (triglyceride levels $\geq 50\%$ above baseline and/or ≥ 2.0 mmol/l). Serum triglycerides remained high (3.7 ± 2.4 mmol/l) during placebo treatment but were reduced after 8 weeks of gemfibrozil treatment ($p < 0.01$). The total cholesterol level decreased slightly ($p < 0.05$) during gemfibrozil treatment, but the LDL/HDL ratio did not change significantly. No untoward effects of gemfibrozil on acitretin dose-response and clinical side-effects were noted. Gemfibrozil thus appears useful in patients prone to retinoid-induced hyperlipidemia unresponsive to dietary treatment and acitretin dose reductions. **Key words:** retinoids; hypolipidemic agents; psoriasis.

(Accepted February 6, 1995.)

Acta Derm Venereol (Stockh) 1995; 75: 377–380.

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Retinoids, i.e. derivatives of vitamin A, have been used in systemic treatment of different skin disorders for about twenty years. Isotretinoin (Accutane®, Roaccutane®) is mostly used for the treatment of severe acne, while etretinate (Tigason®) and acitretin (Neo-Tigason®, Soriatane®) are mainly used in different keratinizing disorders (1). The latter drug has largely replaced etretinate because of more favourable pharmacokinetic properties, particularly its lesser tendency to accumulate in adipose tissue (2, 3).

It has long been known that treatment with oral retinoids may be associated with hyperlipidemia that is reversible after cessation of therapy (4–6). The hyperlipidemic response differs from one patient to the other but seems intraindividually quite constant. Clear-cut elevations in the blood lipid levels may occur in up to 20–25 % of retinoid-treated patients, depending on which group of patients is studied (7). Typical retinoid-induced lipid changes comprise increased triglyceride levels in the very low density lipoproteins (VLDL) and a raised ratio of low density lipoprotein (LDL) to high density lipoprotein (HDL) cholesterol (8). The mechanisms behind these changes are not fully elucidated but probably involve an increased synthesis of VLDL and a reduced clearance of lipids from the blood (7, 9).

Different retinoids may show a slightly different tendency to

induce hyperlipidemia (8). In short-term treatment the lipid changes are probably of minor importance. In long-term treatment, however, these changes are of more concern as they imply an increased risk for the development of atherosclerosis and its complication thrombosis (10, 11). Repeated monitoring of blood lipids is therefore recommended when using retinoids in the treatment of chronic skin disorders, especially in elderly patients who are already at risk for ischemic heart disease.

Several strategies for counteracting retinoid-induced hyperlipidemia have been suggested (for review see ref. 7, 11, 12). First the retinoid dosage should be reduced to a minimum and, if blood lipids remain unacceptably high, dietary advice should be given. If both these measures fail it may become necessary to try some of the lipid-lowering drugs that are available, although their safety and efficacy in retinoid-induced hyperlipidemia remain to be established. Gemfibrozil (Lopid®) is a derivative of valeric acid which has been shown to reduce both the triglyceride and cholesterol levels in patients with idiopathic hyperlipidemia (13).

We describe here a controlled, double-blind study of the effects of gemfibrozil in patients with acitretin-induced hyperlipidemia. To our knowledge no such study has previously been undertaken.

METHODS

Patients

After giving their informed consent 22 patients entered the study (6 women, 16 men). Sixteen patients had psoriasis, 4 palmo-plantar pustulosis, 1 perifolliculitis decalvans and 1 Vohwinkel's syndrome. Nine of the patients had been treated earlier with etretinate, 1 with acitretin and 2 with isotretinoin with good or moderate effects on their skin symptoms but 11 of them had developed retinoid-induced hyperlipidemia. All these patients had been off retinoids for at least 2 months preceding the study. The mean age of the patients was 51.4 years (range 31–72 years) and the mean duration of disease 20.6 years (1–65 years). The mean body weight of the patients was 89 kg (68–180 kg) and their mean Broca's index 1.25 (range 0.88–2.54) (Broca's index = weight (kg)/height (cm) – 100).

Five of the patients had a Broca's index > 1.36 and were consequently regarded as obese. The ingestion of alcohol was occasional in 18 of the patients and regular in 1. Three patients denied use of alcohol.

Five of the 22 patients had hypertension, 2 had angina pectoris, 1 had heart palpitations and 1 had had a cardiac arrest several years earlier. Those treated for concomitant diseases were requested to continue their medication unchanged throughout the study. Of the 14 patients completing the study 2 were on metoprolol, 1 was on propranolol, 1 on isosorbide nitrate and diltiazem, 1 on enalaprilate, and 1 on hormone substitution after ovariectomy. Topical treatment consisted of emollients and occasional corticosteroids; it was not substantially changed during the study.

Clinical Score

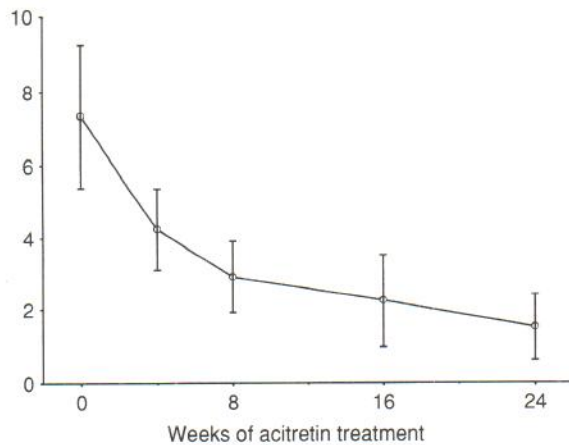


Fig. 1. Mean (\pm SD) clinical scores in 12 patients with psoriasis and palmo-plantar pustulosis completing the whole trial. See text for explanations of scoring and selection of patients. Note the continued clinical improvement during the gemfibrozil/placebo phase of the study.

Design of the study

The trial was performed as an initially open study with acitretin only for 8 weeks, followed by a double-blind cross-over study of gemfibrozil and placebo (8 weeks each), during which a constant dose of acitretin was maintained. At the beginning of the study, a dietician recorded the eating and drinking habits of the patients and, when required, gave instructions about suitable dietary changes. Patients who after 8 weeks of acitretin treatment showed definitely increased (≥ 2.0 mmol/l) triglyceride levels or had a $\geq 50\%$ increase above baseline level (to triglycerides >1.5 mmol/l) continued in the double-blind part of the study and were randomized to receive either gemfibrozil (300 mg \times 2) or placebo (disposed in identically looking capsules) as first treatment. The acitretin dosage, which was initially 40 mg daily (about 0.5 mg/kg) given as 10 mg capsules, was either retained or adjusted to 30–70 mg/day in patients who experienced insufficient clinical effect or intolerable mucocutaneous side-effects after 4 weeks.

Clinical controls were performed before and after 4, 8, 16 and 24 weeks of treatment. Haemoglobin, white blood cell count, platelets, blood glucose, serum bilirubin, creatinine, alkaline phosphatases, aspartate aminotransferase, alanine aminotransferase, cholesterol and triglycerides were analysed at these controls. Lipoprotein analyses were carried out at 0, 8, 16 and 24 weeks.

The study protocol was approved by the Ethical Committee, Faculty of Health Sciences, University of Linköping.

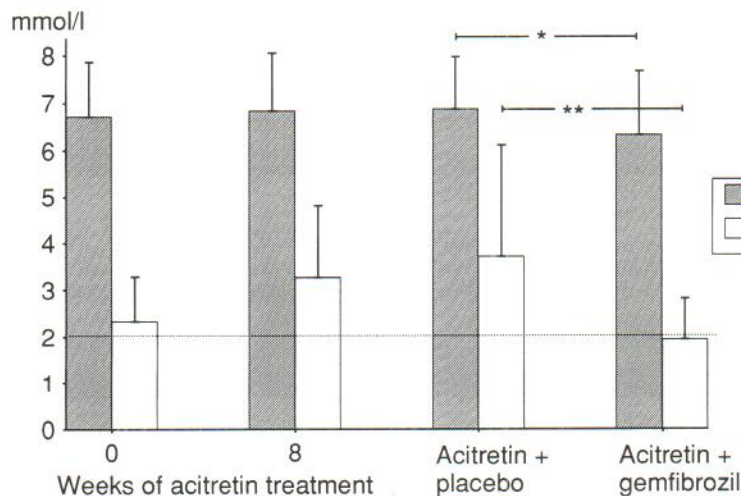


Fig. 2. Mean (\pm SD) concentrations of cholesterol and triglycerides in whole serum ($n=14$) at different time points during acitretin monotherapy and during combination with either placebo or gemfibrozil. The upper normal limit for triglyceride values is indicated by the interrupted line. None of the cholesterol values exceeded the laboratory's normal limit for cholesterol (7.5 mmol/l). Only the significances of difference between acitretin-placebo and acitretin-gemfibrozil are indicated (* $p < 0.05$; ** $p < 0.01$).

Clinical evaluation

The clinical evaluation was performed by the same doctor (CV or AV) in each patient throughout the study. At every visit the clinical symptoms were scored (0–3) for erythema, scaling, palmo-plantar hyperkeratosis and pruritus, using a score value of 3 for severe involvement.

Lipid analyses

Blood samples were drawn from the antecubital vein after an overnight fast. The apolipoprotein E phenotype was determined once using an isoelectric focusing technique (14). Triglyceride and cholesterol concentrations in whole serum as well as in the different lipoprotein fractions were analysed repeatedly by enzymatic and colorimetric methods (Boehringer-Mannheim, Germany). VLDL, LDL and HDL were isolated using a combination of ultracentrifugation and precipitation (15).

Statistics

All treatment periods on gemfibrozil or placebo were pooled regardless of whether they occurred during the first or second double-blind period. The significance of differences between means was evaluated by paired Student's *t*-test.

RESULTS

Clinical effects

Fourteen of the 22 patients completed the trial according to the protocol. One patient left the study after 4 weeks because of mucocutaneous side-effects typical of retinoid therapy, 2 patients left after 8 weeks because of symptoms that may have been aggravated by acitretin (severe sinusitis; haematospermia) and 1 was excluded because of lack of compliance. Four patients were excluded from the double-blind part of the study because their serum triglycerides did not reach the levels stipulated by the inclusion criteria (≥ 2.0 mmol/l or $\geq 50\%$ increase from baseline). The apo E phenotype of these patients was E 3/3 in 2 and E 3/4 in 2. In the patients who developed hyperlipidemia the apo E phenotype varied: 1 had apo E 2/3, 7 E3/3, 2 E4/3 and 4 E3/4.

Five of the patients completing the double-blind cross-over study received gemfibrozil as first drug and 9 placebo. Seven of the 14 patients took 40 mg of acitretin per day for the whole period, 5 had to lower the dose to 30 mg daily and 2 had to increase the dose to 50 or 60 mg daily after 4 weeks to obtain

Table I. Concentrations (mmol/l) of triglycerides (TG) and cholesterol (CHOL) in different lipoprotein fractions (VLDL, LDL, HDL) before and after various treatment (n = 12)

Mean ± SD values

	VLDL TG	LDL CHOL	HDL CHOL	LDL/HDL CHOL ratio
Pre-treatment	1.47±0.70	4.24±0.79	1.01±0.23	4.45±1.46
Acitretin only	2.16±1.04 ^{§a}	4.10±0.89	0.90±0.28 ^{§§}	4.93±1.85
Acitretin-Placebo	2.66±2.02 [§]	4.04±1.05	0.93±0.31	4.60±1.34
Acitretin- Gemfibrozil	1.31±0.82*	3.96±0.80	1.02±0.24	4.17±1.70

a) Significance of difference versus pretreatment values ([§]p < 0.05; ^{§§}p < 0.01) and of difference between gemfibrozil and placebo (^{*}p < 0.05).

good clinical results. There were no further changes in the acitretin medication after this.

Fig. 1 shows the mean clinical score recorded over 24 weeks in 12 patients with psoriasis and palmo-plantar pustulosis. The patients with Vohwinkel's syndrome and perifolliculitis decalvans were excluded from the compilation because of scoring problems; both showed good clinical results. It can be seen from the graph that the patients' skin symptoms improved rapidly during the first 2 months of the study and more gradually so during the gemfibrozil/placebo part of the study. When comparing the individual severity scores after gemfibrozil and placebo, however, we found no difference to suggest that gemfibrozil adversely affected the clinical response to acitretin (data not shown). Similarly, there were no side-effects (mucocutaneous dryness, skin peeling, hair loss) predominantly appearing during gemfibrozil-acitretin treatment. Except for blood lipid elevations (see below) there were no persistent changes in routine laboratory tests in any of the groups.

Lipid changes

Results are only presented for patients completing the whole study (NB lipoprotein analyses incomplete in 2 patients).

Whole serum. Fig. 2 shows the mean (± SD) triglyceride and cholesterol concentrations during the first 8 weeks of acitretin therapy and after the two double-blind periods of additional treatment. The mean triglyceride concentration, which was slightly above the upper normal limit before therapy, increased by 40% (to 3.27 mmol/l) during the first 8 weeks of treatment (p < 0.01) and by a further 19% (to 3.71 mmol/l) during the acitretin-placebo period. During acitretin-gemfibrozil treatment the triglyceride values fell significantly (p < 0.01 compared to the acitretin-placebo period) to levels well below pretreatment values.

The cholesterol concentrations seemed rather constant during the study but were actually significantly reduced during acitretin-gemfibrozil treatment as compared to acitretin-placebo (p < 0.05).

Lipoproteins. Table I shows the mean concentrations of triglycerides and cholesterol in different lipoproteins before and after the various treatments. Although triglycerides and cholesterol were analysed in all lipoprotein fractions (VLDL, LDL and HDL), only the most characteristic results are shown. It can be

seen that the VLDL triglyceride concentration, which was 81% above baseline during acitretin-placebo therapy, reverted to well below (minus 11%) pretreatment level during gemfibrozil treatment.

The LDL cholesterol concentration decreased slightly during the first 8 weeks of acitretin treatment and fell further during gemfibrozil and placebo therapy. The HDL cholesterol values which were about 10% below the pretherapy level during acitretin (± placebo) treatment returned to pretherapy level after gemfibrozil was given. As a result, the LDL/HDL cholesterol ratio decreased although not significantly so.

The individual variations in lipid levels during acitretin-placebo and acitretin-gemfibrozil were not distinctly related to either the apo E phenotype or the pretherapy lipid levels (data not shown).

DISCUSSION

The patients entering this study were selected because they were at increased risk of developing hyperlipidemia during acitretin therapy. Thus 11 of the patients had a previous history of retinoid-induced hyperlipidemia and 4 had pre-existing endogenous hyperlipidemia. Nonetheless, only relatively few patients developed clear-cut hyperlipidemia during the first 8 weeks of therapy, and some patients even showed decreased lipid levels. This was surprising in view of the fact that 4–8 weeks of retinoid therapy is usually sufficient to produce steady state levels of increased serum triglycerides. Probably, the incidence of hyperlipidemia was reduced by the dietary advice given at the outset of the trial. It is our impression that many patients enthusiastically complied with the dietary instructions during the first part of the study. Later on, however, several apparently failed to do so possibly because they were confident that the lipid-lowering drug would be efficient enough. This may somewhat have distorted the results of the double-blind phase and is the most likely explanation why triglyceride levels were higher during acitretin-placebo treatment than during acitretin therapy alone (see Fig. 2).

By and large, the lipid changes seen in this long-term study of acitretin are in concordance with previous experience with oral retinoid therapy (4, 5, 16); i.e. patients tend to develop increased triglyceride levels (mainly due to an increased VLDL fraction), slightly increased total cholesterol and an increased LDL/HDL cholesterol ratio. It would certainly be of great value if there was a way to predict which patients will develop these lipid changes. In an attempt to see if the apolipoprotein E phenotype was prognostic, we screened our patients for this variable but found no phenotypic pattern that could predict later development of acitretin-induced hyperlipidemia.

During gemfibrozil treatment there was a dramatic fall in total triglycerides, also reflected in the VLDL triglycerides (see Fig. 2 and Table I). The total serum cholesterol level did not change much numerically, but the decrease during gemfibrozil treatment was statistically probably significant (p < 0.05). Interestingly, all lipid variables including the LDL/HDL cholesterol ratio were at a more favourable level during acitretin-gemfibrozil than before acitretin therapy, suggesting that gemfibrozil not only counteracted the retinoid-induced hyperlipidemia

but also reduced coexisting endogenous hyperlipidemia if present.

Gemfibrozil is supposed to decrease the synthesis of VLDL particles and increase the clearance of lipoprotein particles from the circulation (13). The drug is well absorbed from the gut and is largely bound to plasma proteins (17). The high affinity of gemfibrozil to plasma proteins implies a theoretical risk for interference with other lipophilic drugs (e.g. retinoids), possibly resulting in an altered dose response. Also, there have been claims that gemfibrozil treatment per se may deteriorate the skin symptoms in psoriatic patients (18), although this was later questioned (19). We monitored the clinical score and side-effects of the acitretin-treated psoriatics in a double-blinded manner during gemfibrozil/placebo treatment and were unable to observe any untoward effects that could be ascribed to gemfibrozil.

It may well be questioned whether it is medically, ethically and economically justifiable to treat a non-malignant skin disorder like psoriasis with two drugs, gemfibrozil and acitretin, both being expensive and potentially hazardous. The answer cannot be straight-forward and omnidirectional. Several factors have to be considered before starting such a combined treatment. The age of the patient and occurrence of concomitant diseases (hypertension, ischemic heart disease etc) are certainly important factors. Also, the need for continued long-term retinoid treatment must be imperative, and the serum lipid elevations should be marked (e.g. triglyceride levels exceeding 2.5 mmol/l) and unresponsive to dietary advice. In such cases we have found gemfibrozil to be a safe and effective treatment for retinoid-associated hyperlipidemia.

ACKNOWLEDGEMENTS

The valuable assistance of Mr C. Collin (Roche AB, Stockholm) in planning this study is gratefully acknowledged. We also want to thank our dietician, Mrs Elsy Edholm, and the staff at the Departments of Dermatology and Medicine for valuable assistance. The study was made possible through grants from Hoffmann-LaRoche AG and the Swedish Medical Research Council. The gemfibrozil and placebo capsules were kindly supplied by Park-Davies Ltd.

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