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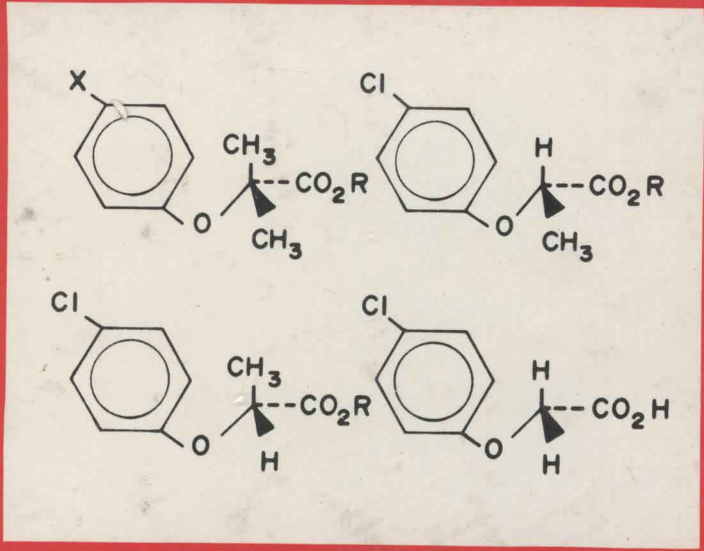


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# CLOFIBRATE AND RELATED ANALOGS

## A Comprehensive Review

# Clofibrate and Related Analogs

*A COMPREHENSIVE REVIEW*

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To our graduate students and postdoctoral

research associates, both past and present,

and especially

to our wives

Deanne

Pauline

Grace

## PREFACE

Coronary or other arterial vascular disease are major causes of death in Western Society. Hyperlipoproteinemia is a recognized risk factor associated with clinical manifestations of atherosclerotic lesions in arteries. For many years chemical agents have been utilized to modify or correct hyperlipoproteinemic states in patients. Since its discovery in 1962, clofibrate [ethyl 2-(4-chlorophenoxy)-2-methylpropionate] represents one major prototype drug which has been useful in the treatment of this disease entity. The main purpose of this monograph is to present a comprehensive review of the pharmacological and clinical studies completed with clofibrate and structurally related aryloxy agents.

A multitude of scientific data pertaining to the hypolipidemic properties of clofibrate and structurally related agents has been accumulated in human patients and experimental animal models. We find that the majority of information on these hypolipidemic agents has been derived by the combined efforts of scientists in the areas of pharmacology, physiology, biochemistry, endocrinology, molecular biology, pathology, medicinal chemistry and clinical pharmacology. Clearly, no other hypolipidemic agent has been as extensively studied by so many investigators in various scientific disciplines. Even so, definitive information on the relationship between the biochemical interaction at specific tissue or subcellular site(s) and the observed hypolipidemic properties of clofibrate is far from complete. In many cases, the evidence presented is more suggestive than certain. Related to the antilipidemic properties of clofibrate we discuss effects on fatty acid, triglyceride, cholesterol, and lipoprotein metabolism, lipoprotein lipase activity and lipolysis in adipose tissue. In this monograph, we also summarize those findings with clofibrate and related aryloxy analogs



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which may not be directly responsible for their hypolipidemic activities. For example, considerable information concerning the structure-activity-relationships of clofibrate on the activities of specific enzymes contained within the subcellular organelles of mitochondria, microsomes and microbodies (peroxisomes) has emerged in recent years. Other topics discussed include clofibrate effects on cholesterol ester composition and metabolism, protein binding and antithrombotic actions and modification of endocrine function.

For many years we have been interested in stereochemical aspects of clofibrate-induced antilipidemic activity. We hope that this monograph will be beneficial to scientists dedicated to the elucidation of the biological mechanisms of action and design of hypolipidemic agents.

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## ABBREVIATIONS

Ac, acetate; ADH, antidiuretic hormone; ADP, adenosine diphosphate; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; ATT, arginine tolerance test; BSA, bovine serum albumin; CAD, coronary artery disease; cAMP, cyclic 3',5'-adenosine monophosphate; CD, chemical diabetes; CHOL, cholesterol; CI, cerebral infarct(s); CPK, creatine phosphokinase; DDAVP, 1-deamino-8-D-arginine vasopressin; D-$T_4$, dextrothyroxine; E, epinephrine; FA, fatty acid(s); FFA, free fatty acid(s); GC, gas chromatographic; GFR, glomerular filtration rate(s); GH, growth hormone; GI, gastrointestinal; $\alpha$-GPD, $\alpha$-glycerophosphate dehydrogenase; GTF, glucose tolerance factor; HBABA, 2-(4'-hydroxybenzeneazo)benzoic acid; HDL, high density lipoprotein(s); HGH, human growth hormone; HMGCoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HSA, human serum albumin; IDL, intermediate density lipoprotein(s); IRG, immuno-reactive glucagon; LCAT, lecithin: cholesterol acyltransferase; LDL, low density lipoprotein(s); LPL, lipoprotein lipase(s); MCTG, medium chain triglyceride(s); MVA, mevalonate; NE, norepinephrine; OGTT, oral glucose tolerance test(s); osm, osmolality; PB, protein bound; PHLA, post-heparin lipoprotein lipase activity; PL, phospholipid(s); RSA, rat serum albumin; SER, smooth endoplasmic reticulum; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvate transaminase; Sosm, serum osmolality; $T_4$, L-thyroxine; TBG, thyroxine binding prealbumin; TG, triglyceride(s); TIA, transient ischaemic attacks; Uosm, urine osmolality; and VLDL, very low density lipoprotein(s).

# Clofibrate and Related Analogs

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## INTRODUCTION

Subsequent to the 1962 report by Thorp and Waring (1) showing that clofibrate [ethyl 2-(4-chlorophenoxy)-2-methylpropionate; I] administration reduced serum and liver cholesterol (CHOL) concentration in both intact and gonadectomized rats, numerous studies were initiated to determine the mode of action and clinical efficacy of this drug. Initial studies in animals (1,2) involved use of a mixture of clofibrate and androsterone, and for these reasons early clinical investigations (3) also utilized the clofibrate-androsterone mixture. Oliver's studies revealed that the mixture produced a significant continued depression of serum CHOL, triglycerides (TG) and uric acid in 19 of 20 hypercholesterolemic patients with ischaemic heart disease; in similar patients, neither androsterone nor clofibrate alone produced any significant effect (3). However, as pointed out by Pinter (4) subsequently, the effect of clofibrate on lowering elevated CHOL and TG levels in some 1300 hypercholesterolemic patients was observed; these results were discussed in the well known Buxton, England symposium on clofibrate (5).

Early results utilizing animals also were difficult to interpret. For example, in monkeys fed a biscuit formulation of ground wholewheat (50%), dried whole milk (30%), fresh whole egg (10%), malt extract (7.5%), dried yeast (2%), and salt (0.5%), and supplemented with Vitamins A, C, and D, clofibrate caused a rise in serum CHOL, whereas androsterone was inactive and a mixture of clofibrate (100 mg/kg) and androsterone (2.5 mg/kg) caused a marked fall in serum CHOL (2). Similar results were observed for the mixture utilizing monkeys fed a relatively low fat diet (2).

In addition, the literature concerned with the biological properties of clofibrate in small animals is filled with conflicting results. Clo-



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fibrate is reported not to inhibit (1) and to inhibit (6,7) the acute hypertriglyceridemia and hypercholesterolemia in rats administered Triton WR-1339 by iv or ip injection. Additionally, whereas clofibrate was found to be effective in normal rats, it intensified hypercholesterolemia in the CHOL-fed chicken or monkey (1) and had little or no effect upon the plasma CHOL levels of CHOL-fed rabbits (8). Further, early observations in rats (1) indicated that clofibrate did not increase the rate of inactivation of a barbiturate; later several investigators (9-12) demonstrated an increase in liver weight, microsomal protein content and metabolism of pentobarbital and zoxazolamine after clofibrate administration. As pointed out by Byers and Friedman (13), there were even greater divergences of opinion concerning the effect of clofibrate upon TG metabolism in the rat. Thus, Thorp and Waring (1) and later Best and Duncan (14) concluded that clofibrate lowered plasma TG levels in the rat, whereas Kokatnur et al. (15) and Azarnoff et al. (16) found clofibrate either had questionable activity or no effect on serum TG levels in this animal. Many additional conflicting results will be discussed throughout this review.

The clofibrate story is far from complete. Nonetheless, since 1962, many advances have been made in our understanding of the biological properties of this rather simple aryloxy ester. Perhaps no molecule has captivated the imagination of so many scientists in so many different fields in so short a period of time. Serving as a lead compound, clofibrate had provided the basis for drug design and numerous structure-activity studies of antilipidemic drugs, as well as investigations of mechanism of action and the relationship of physico-chemical properties to biological activity. For these reasons, the authors considered that a comprehensive review of the biological properties of clofibrate and closely related analogs coupled

with a discussion of modes of action and clinical efficacy of clofibrate and related analogs to be particularly timely. Additionally, several other reviews, generally emphasizing different aspects of hyperlipidemia, are available in which clofibrate and related analogs have been discussed (17-39).

## CLINICAL STUDIES

### Efficacy in lowering lipid levels

In clinical studies clofibrate has been effective in lowering patient TG levels to 15-60% of placebo controls (40-64). This effect appeared to be extended by clofibrate given in combination with gonadotropin (53) and by clofibrate given with dextrothyroxine (D-$T_4$) (65). The only exception was complete lack of TG lowering in an older group of senile and brain-damaged subjects (51). The response to clofibrate when efficacious appears to be maximal at 1 yr, and at that point TG concentration plateaus at a new steady state level (66).

The efficacy in lowering serum CHOL is less dramatic (11-57%) (40-64, 67-70). In the Coronary Drug Project (66) in which the largest group of patient data have been analyzed, CHOL concentration means were reduced 7.2%. TG concentration was lowered 23% (66). Based on the TG to CHOL ratio of 5 in very low density lipoproteins (VLDL) (71), a majority of the CHOL lowering could be attributable to reduction in VLDL, but 36% of the reduction in CHOL concentration was most likely due to reductions in the concentration of other lipoproteins. This finding is even more striking in the United Airlines study in which 53% of the reduction in CHOL concentration could be computed to be due to the reduction in lipoproteins other than VLDL (72).

Caganova and Cagan (73) found that administration of 500 mg/8 hr of clofibrate for 6 mo, and then 500 mg/6 hr of clofibrate for 6 wk, caused an initial and then an additional decrease in serum lipids. This decrease could be maintained by reducing the dose to 500 mg/8 hr. Cottet et al. (74), with 18 hyperlipidemic patients, claimed an improved regimen for clofibrate administration. These investigators dispensed 3 g/day until an optimal hyperlipidemic effect was found and then administered the drug at 3 g/every other day. Under these conditions the serum CHOL concentration was lowered 13% and TG concentration was lowered 36%. Berkowitz (75) treated 50 hyperlipidemic patients, 8 of whom had essential hypercholesterolemia, with clofibrate (2 g/day), which normalized the CHOL concentration and reduced the serum TG concentration by a minimum of 25% in 8 yr of administration. During this period significant improvements in glucose tolerance were observed in 24 of 36 patients who had originally shown abnormal glucose tolerance. Berkowitz found that TG elevations were in proportion to glucose intolerance (75).

Levy et al. (76) showed that in selected patients with all phenotypes where 2 g/day of clofibrate was administered, no effects were observed with Type I hyperlipoproteinemia. For Type II hyperlipidemic patients, clofibrate caused a mean fall in plasma CHOL level of 9% and overall did not cause xanthomas to regress. Cholestyramine, in dosages of 16-24 g/day, exhibited a much greater effect than clofibrate (76). In heterozygous familial Type II children, clofibrate (18-20 mg/kg body wt/day) and corn oil diet combination reduced CHOL 33% (77). However, West and Lloyd (78) found that in similar children treated for 3 yr with a low-saturated fat diet and clofibrate, there was little adherence to either dietary or drug regimen. This was partly due to the minimal reductions observed in serum

CHOL concentration.

For Type III hyperlipoproteinemia, clofibrate reduced the plasma CHOL and TG levels by 35 and 45%, respectively. Feeding 2 g/day of clofibrate to a patient with broad-β disease (Type III), who was on a diet of either normal or fat-free composition, caused serum lipoproteins to be modified so that there was a reduction in the relative proportion of the electrophoretically faster migrating more TG-rich lipoprotein and an increase in the slower migrating more CHOL-rich species (79). Azarnoff (80) concluded that clofibrate has maximum effectiveness in Type III patients.

Lees and Wilson (81) have shown that there is a significant relationship between low density lipoproteins (LDL) and VLDL with clofibrate therapy. They also showed that LDL CHOL doubled for 4-5 subjects with Type IV and Type V hyperlipoproteinemia, but no such reciprocity occurred in Type III patients. The inference of this study is that the drug treatment might increase rather than decrease atherogenic risk. Conversely, Brown et al. (82) showed a high correlation between CHOL lowering and LDL reduction with clofibrate treatment.

Miettinen et al. (83) showed that clofibrate treatment in Type IV patients gave 128% reduction in TG and 9% reduction in serum CHOL concentrations. β-lipoprotein, immunologically determined, dropped 13%. A rise in percentage of α- and β-lipoproteins, with losses in pre-β-lipoproteins, was found (83). In a large clinical study, Smith et al. (84) treated 150 Type IV subjects, on identical regimens and without intervention, with special diets for 6 wk and clofibrate (4 g/day) plus the calorie-controlled diet for 18 wk through private physicians. Under the direction of the private physician, diet alone reduced TG 42% and CHOL 6.5%. With clofibrate

added to diet, there was only an additional 8% reduction in TG and no further reduction in CHOL concentration. Patients on this regimen who were followed by these investigators showed greater CHOL and TG lowering than the physician-followed subjects. The CHOL lowering in the first 6 wk was 11% with no significant change after 6 wk of clofibrate treatment and a slight rebound after 24 wk of the combined diet and clofibrate. TG was reduced by 50% after 6 wk of diet. Six additional wk of combined therapy using diet and clofibrate reduced TG another 12% with no further change in the remaining 12 wk of the combined regimens (84). Clofibrate is therapeutic for Type IV disease, but dietary restrictions should be tried first (85). Zelis et al. (86), with 12 Type IV patients treated with clofibrate (2 g/day) or corn oil placebo in a randomized double-blind study for 28 days, followed by crossover to an alternative substance, found that the overall TG reduction with clofibrate was 40%.

Mixed hyperlipoproteinemia $II_b$ treated with clofibrate gave 11-13% decreases in total CHOL and 17-29% decreases in total TG (83,87). Olsson et al. (87) also observed that in Type $II_a$ patients, treatment for 3 mo with 1.5 g/day of clofibrate lowered TG serum concentration 31% and CHOL serum concentration 20%. Gustafson and Lanner (88), with 11 patients having Type $II_a$ hyperlipoproteinemia, 6 of whom were familial, instituted treatment with Secholex (DEAE-Sephadex) or clofibrate. Clofibrate gave an average serum CHOL lowering of 6%, whereas Secholex alone reduced CHOL concentration 17%. (For discussion of these drugs in combination, see Efficacy in lowering lipid levels in combination with other drugs.)

Type IV patients, treated with clofibrate, had a modest lowering of TG, but no effect on carbohydrate-induced hypertriglyceridemia was observed. For Type V patients clofibrate had no significant effect on serum TG or

CHOL levels (76,89). Similar findings were described by Schlierf and Kahlke (90). Crepaldi et al. (91) found that long term clofibrate treatment reduced serum CHOL levels 20% in Type II patients and about 30% in Type IV-V patients. TG were reduced 60-70% in Type IV patients (91). Casdorph (92) concluded that clofibrate is 1) the last to be used in Type II hyperlipoproteinemics, 2) uniformly successful in Type III hyperlipidemics, and 3) the treatment of choice in Type IV patients. Clofibrate sometimes is effective in Type V hyperlipoproteinemic patients.

Measurement of lipoproteins in the Newcastle study showed that both LDL and VLDL were reduced with clofibrate treatment (93). In contrast, the direct measurement of $S_f$20-105 (VLDL) and $S_f$0-20 (LDL) protein concentrations by Strisower (94-96) showed that clofibrate reduced VLDL 55% but had no effect on LDL. LDL was lowered only when clofibrate was administered in combination with thyroxine ($T_4$) (85). In later studies, Strisower (85) concluded that Type $II_a$ disease is amenable to clofibrate therapy, since the $S_f$0-20 reductions range from 20-25% after clofibrate administration. However, Type $II_b$ patients were found to be refractory to clofibrate or tolbutamide. Scott et al. (97), in 52 patients with Type $II_a$ hyperlipoproteinemia who were treated with clofibrate, demonstrated persistently lowered LDL levels. A somewhat different set of findings was seen by Rose et al. (98) when they determined CHOL and TG in individual lipoprotein species before and after clofibrate treatment. These investigators found that clofibrate alone reduced both TG and CHOL in Type $II_b$ hyperlipoproteinemia and this primarily was reflected in a VLDL lowering, although some reduction in LDL CHOL was also noted. The Type IV patients had elevations in LDL CHOL concomitantly with VLDL TG and CHOL lowering. Clofibrate in combination with colestipol effectively

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