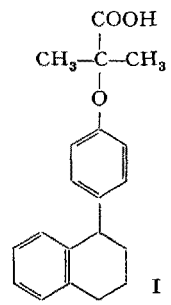
Hypolipidaemic Properties of a New Tetralin Derivative (CIBA 13,437-Su)

The recognition of hyperlipidaemia as one of the main factors associated with atherosclerosis has renewed interest in the use of orally active, non-steroid lipid-lowering agents[1–4]. Phenolic ethers, in particular, represent one broad group of chemical substances which have been investigated in this respect[5–8].

The present communication reports on the hypolipidaemic activity of the tetralin derivative, 2-methyl-2-[*p*-(1,2,3,4-tetrahydro-1-naphthyl)phenoxy]-propionic acid (I), CIBA 13,437-Su. The substance was prepared in the following way. Phenol was alkylated with 1,2,3,4-tetrahydro-1-naphthol under the conditions of the Friedel-Crafts reaction. The resulting *p*-substituted phenol was converted to its sodium salt and etherified with ethyl α-bromoisobutyrate to afford the ethyl ester of (I), b.p. 198 °C/0.4 mm. Hydrolysis of the ester in methanotic potassium hydroxyde solution furnished the acid (I), m.p. 127–128 °C.



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The decrease of the plasma concentration of cholesterol and lipids as affected by CIBA 13,437-Su was not associated with systemic alterations at effective dose levels and appeared to be devoid of gross endocrine manifestations.

The lipid-lowering properties of CIBA 13,437-Su were investigated in intact male albino rats weighing about 200 g, which were kept on a standardized diet (fat content approximately 5% by weight).

The compound was administered in polyethylene glycol by gavage once daily and after 7 and 14 days, total serum cholesterol was determined in orbital blood[9]. Serum free and esterified glycerol was measured[10] in the same animals after a further dose and following a 20-h fasting period, and also in fed rats in which hyperglyceridaemia was produced by administering 10% fructose for 24 h in their drinking fluid[11]. Additional experiments with CIBA 13,437-Su were carried out in male beagle dogs. The dogs received the compound daily in capsule form. In this species, serum cholesterol was determined at weekly intervals in venous blood according to NESS et al.[12].

For the measurement of liver constituents in rats, a 1:5 (w/v) homogenate was prepared in 1.15% KCl, which served for the determination of free and esterified cholesterol[13], glyceride-glycerol[10], lipid-phosphorus[14], glycogen[15] and protein[16]. Significance of difference was ascertained with the *t*-test.

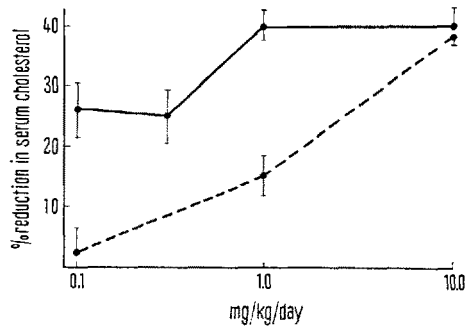
In rats, a significant cholesterol-lowering effect was obtained after 1 week of treatment with 1 mg/kg/day of CIBA 13,437-Su. However, by extending the treatment to 14 days, the effect of lower dose levels was more pronounced and following the same dose of 1 mg/kg a near maximum response occurred (Figure). The effect of the 14-day treatment was reversed within 14 days after withdrawal of the drug. The activity of CIBA 13,437-Su proved to be higher than that of various other known hypocholesterolaemic compounds with the exception of an oestrogenic preparation (Table I).

Serum glyceride levels were markedly lowered by CIBA 13,437-Su at 10 mg/kg/day both in fasting animals and

Table I. Hypocholesterolaemic effect of various agents in the rat[a]

Compound	Dose (mg/kg/day)	Effect (%)	Significance *P*
Premarin®	1	− 54	< 0.001
L-Thyroxine	1	− 16	< 0.01
17α-Methyl-testosterone	10	− 18	< 0.01
Atromid-S®[b]	30	− 17	< 0.01
	100	− 33	< 0.001
	300	− 38	< 0.001
Nicotinic acid	300	− 22	< 0.001
CIBA 13,437-Su	1	− 40	< 0.001

[a] Male rats (10 animals/group) treated for 14 days. Hypocholesterolaemic effect expressed as % difference from initial value. [b] Ethyl 2-(*p*-chloro-phenoxy)-isobutyrate.



Cholesterol-lowering effect of CIBA 13,437-Su in the male rat (n = 10) following a 7-day (– – –) and 14-day (——) period of treatment. (Means ± S.E.).

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Table II. Serum glyceride-lowering effect of CIBA 13,437-Su in the fasting and in the hyperglyceridaemic rat

Group	No. of rats	Glyceride-glycerol *m* Mol/l (mean ± S.D.)	Difference %	Significance *P*
20 h after fasting	9	1.48 ± 0.65	− 54	< 0.001
20 h after fasting + 13,437-Su	10	0.68 ± 0.18		
Fructose	5	2.94 ± 1.26	− 49	< 0.01
Fructose + 13,437-Su[a]	5	1.50 ± 0.44		

[a] Treatment with 10 mg/kg/day for 3 days prior to the addition of fructose (10% in drinking water). For other conditions, see text.

Table III. Changes in constituents of liver[a] from male rats[b] treated with CIBA 13,437-Su

	Controls mean ± S.D.	Treatment for 7 days			Treatment for 14 days		
		mean ± S.D.	% difference	Significance *P*	mean ± S.D.	% difference	Significance *P*
Liver weight g/100 g body weight	4.3 ± 0.3	8.0 ± 0.3	+ 86	< 0.001	8.6 ± 0.8	+ 100	< 0.001
Protein	172.2 ± 19.5	220.2 ± 10.4	+ 28	< 0.001	251.2 ± 8.4	+ 46	< 0.001
Glycogen	21.5 ± 3.1	6.1 ± 1.2	− 72	< 0.001	7.1 ± 2.4	− 67	< 0.001
Glyceride-glycerol	12.4 ± 2.2	7.1 ± 0.4	− 42	< 0.001	8.1 ± 1.9	− 35	< 0.001
Total cholesterol	2.4 ± 0.2	1.6 ± 0.1	− 34	< 0.001	1.8 ± 0.2	− 25	< 0.001
Cholesterol esters	0.7 ± 0.2	0.3 ± 0.1	− 53	< 0.001	0.4 ± 0.1	− 41	< 0.01
Phospholipid	40.9 ± 3.4	43.7 ± 3.4	+ 8	> 0.1	42.4 ± 4.2	+ 4	> 0.4

[a] mg/g of wet weight. [b] 5–6 animals/group, which were kept on standard diet ad libitum and were treated with 100 mg/kg/day.

in fed rats receiving fructose (Table II). There was practically no effect on the free glycerol content of serum.

In male beagle dogs a mean reduction in serum total cholesterol of 20% occurred at 1 mg/kg/day and this cholesterol-lowering effect was increased to 32% by administering 2 mg/kg/day for 3 weeks.

Following treatment with CIBA 13,437-Su no sterol other than cholesterol was found in the serum extracts[17].

Following repeated oral administration at high dose levels, the only apparent effect of CIBA 13,437-Su on the various organ systems was that of liver hypertrophy in rats. An increase in liver weight (absolute and relative to body weight) was noted in the male rat following a threshold dose of 10 mg/kg/day and, following 100 mg/kg/day, the liver weight reached a maximum of twice the control value after 14 days of treatment. This hepatomegalic effect was of a 'proportionate' kind in that the change in weight was not attributable to one main tissue constituent (Table III). CIBA 13,437-Su resulted in a significant reduction in glycogen, total glyceride and cholesterol concentration/g liver. Owing to the increase in organ weight, however, free cholesterol content per whole liver was increased (from a control mean of 19.6 ± 1.0 mg to 27.3 ± 4.2 mg and 35.3 ± 4.6 mg in the treated groups). Protein concentration was increased both in relative and in absolute terms. This behaviour of liver constituents is suggestive of an adaptive type of hypertrophy with enlargement of hepatocyte cytoplasm[18]. In the rat, this was confirmed morphologically and preliminary findings suggest a close similarity to the effects of other aryloxy compounds[19]. The hepatomegalic effect was fully reversible upon withdrawal of the drug.

CIBA 13,437-Su was found to be devoid of any endocrine activity of its own and, in particular, to lack oestrogenic properties[20]. In rats, the actions of the compound were sex-dependent and no significant hypocholesterolaemic nor hepatomegalic effect was produced in female animals at 10 mg/kg/day.

However, in castrated-adrenalectomized male rats, a highly significant cholesterol-lowering (− 32%) and glyceride-depressant (− 62%) effect was obtained at this dose level, indicating that the action of the drug was not dependent on any potentiation of endogenous steroid hormones.

Zusammenfassung. 2-Methyl-2-[*p*-(1,2,3,4-tetrahydro-1-naphthyl)-phenoxy]-propion-säure (CIBA 13,437-Su) stellt ein oral aktives Tetralin-Derivat dar, welches ausgeprägte Blutlipid-senkende Eigenschaften besitzt. Die hypolipidaemische Wirkung wurde bei mehreren Spezies untersucht und umfasste sowohl Cholesterin wie Glyzeride.

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