Henry Ford Hospital Medical Journal

Volume 13 | Number 4 Article 7

12-1965

Treatment Of Hyperlipidemia With The Ethyl-ester Of Chlorophenoxyisobutyrate And Androsterone

Irwin J. Schatz

Henry Ford Hosp. Med. Bull.
Vol. 13, December 1965

TREATMENT OF HYPERLIPIDEMIA WITH THE ETHYL-ESTER OF CHLOROPHENOXYISOBUTYRATE AND ANDROSTERONE

IRWIN J. SCHATZ, M.D.

From the Section of Peripheral Vascular Disease,
Henry Ford Hospital, Detroit, Michigan

The etiology of atherosclerosis is unknown, but a preponderance of clinical, epidemiologic, and experimental evidence supports the thesis that in man elevated plasma lipids play a role in its development.[1] Accordingly, some clinicians have concluded that lowering the level of blood fats in patients is an important step in the prevention and treatment of atherosclerotic vascular disease. The relationship between plasma lipids and atherosclerosis is presumptive only; attempts to lower plasma lipids in man have not been proved to prevent or revert atherosclerosis. Nevertheless, as Margaret Albrink has said, "Although a 100 per cent certainty does not exist, somewhere along the line the results of medical research have to be translated into recommendations for action."[1]

Many methods of lowering blood fat levels have been devised; the most effective and commonly used of these is manipulation of the amount and type of dietary fat. Occasionally however, alternative forms of treatment are needed, mainly because patients find it difficult to follow dietary instructions conscientiously or because the diet itself has failed to lower the blood fats. Consequently, a multitude of oral medications have been recommended as hypolipemic drugs. Over fifty of these compounds have been described,[2] but none of them has proved ideal. Thus the search for a safe and efficacious drug continues.

It is known that hormonal factors play a role in the normal variation of serum cholesterol in both animals and man. Recently, a series of simple modified estrogen compounds (aryloxyisobutyric acids) were administered to animals; the effect on serum lipids was studied.[3] The most powerful of these in lowering the cholesterol was the ethyl-ester of chlorophenoxyisobutyric acid (E-CPIB).

A spontaneous rhythmic decrease in serum cholesterol is observed normally in rats, and also occurs in the human.[4] This is accompanied by increased adrenal cortical and thyroid activity. Since thyroid hormone increases androsterone levels, and it is

known that androsterone is hypocholesteremic,[5] it has been postulated that androsterone might be the endogenous agent which is responsible for phasic changes in cholesterol.

When androsterone is given to man parenterally it lowers cholesterol, but the side-effects of its administration are intolerable. When administered orally in man it is ineffective, apparently because of inactivation in the gastrointestinal tract. However, with E-CPIB with androsterone is given by mouth hypolipemia results; it is not clear if E-CPIB facilitates the absorption of androsterone, but it is known that the metabolic action of androsterone is potentiated, perhaps because E-CPIB displaces androsterone or its conjugate from plasma proteins. It is possible that increased amounts of androsterone accumulate in the liver where its action on hepatic fat synthesis results in decreased plasma lipid levels.[6]

Obviously, clinical evaluation of this substance is warranted and several reports of its efficacy in the treatment of hyperlipidemic states have appeared.[6,7,8] No androgenic side-effects have been noted either in animals or in man after administration of this compound.

In view of its possible therapeutic value, study of E-CPIB-androsterone* was made in a group of outpatients with elevated plasma lipids at the Henry Ford Hospital.

Material and Method

Twenty-six outpatients with elevation of plasma lipids volunteered for this study. They were part of a group of outpatients referred for evaluation and treatment of various hyperlipidemic states. The only criteria for inclusion in this study were the repeated demonstration of elevated levels of plasma lipids and the willingness of the patient to participate in a prolonged clinical experiment. Fourteen of this group had atherosclerotic vascular disease (Table 1). Multiple control measurements of cholesterol, triglycerides and total lipids were made in the postabsorptive state (thirty to ninety minutes after eating) during a one to six week period before therapy was started, and subsequently every three to four weeks during treatment. Multiple measurements on the same samples as well as on samples drawn ten minutes apart were made intermittently during the course of therapy. Serum glutamic oxolacetic transaminase (SGOT), leukocyte count, and alkaline phosphatase were measured before treatment and then monthly thereafter; in selected patients uric acid, serum protein electrophoresis, and bromsulphalein dye retention also were determined monthly. After three months of therapy smears of the peripheral blood of each patient were examined; subsequently this was done monthly. The patients were instructed to make no alteration in their activities, or medications, except for anticoagulant drugs when necessary. Two patients with diabetes mellitus continued to adhere to the recommended diabetic diet without any major changes during the course of treatment. Other patients

*Provided as Atromid by John B. Jewell, M.D., Vice President and Medical Director, Ayerst Laboratories, New York City, New York.

Table I

Patient	Age	Sex	Diagnosis	Pretreatment Levels*		
				Cholesterol	Triglycerides	Total Lipids
				Normal** (140-280 mg. per cent)	Normal** (40-120 mg. per cent)	Normal** (up to 850 mg. per cent)
T.W.	47	M	Hypertension	307	241	1765
H.S.	56	M	Generalized Atherosclerosis	408	308	1466
A.S.	37	M	Healthy	436	738	2316
W.Z.	51	M	Generalized Atherosclerosis	432	1025	3979
G.G.	29	M	Healthy	376	66	867
L.K.	36	M	Diffuse Atherosclerosis	362	67	908
F.D.	56	M	Healthy	342	100	953
S.S.	38	M	Coronary Atherosclerosis	447	53	1249
F.F.	42	M	Healthy	350	74	841
M.H.	43	F	Pre-Menopausal; Myocardial Infarction	245	126	796
Q.B.	55	M	Coronary Atherosclerosis	273	178	840
P.Z.	45	M	Coronary Atherosclerosis	249	264	988
A.S.	48	M	Coronary Atherosclerosis	273	185	929
C.J.	52	M	Coronary Atherosclerosis	335	138	799
J.F.	51	M	Healthy	312	124	914
E.F.	52	F	Coronary Atherosclerosis	327	220	1218
R.S.	47	M	Healthy	290	152	968
D.T.	57	F	Diabetes Mellitus	320	386	1238
J.H.	43	M	Coronary Atherosclerosis	305	142	909
D.D.	57	M	Healthy	333	173	1036
L.B.	55	M	Healthy	300	128	964
R.F.	46	M	Coronary Atherosclerosis	265	252	1030
L.S.	56	M	Diabetes Mellitus Generalized Atherosclerosis	252	1015	1630
K.M.	47	M	Coronary Atherosclerosis	256	479	1195

**Precision of determination for 95 per cent reliability:
cholesterol: ±8 per cent
triglycerides: ±8 per cent
total lipids: ±10 per cent.
*All values are means of multiple measurements.

were requested to adhere to their regular dietary habits and make no significant changes in the amount or type of fat or the number of calories taken. Thus, if a low fat diet had been followed prior to therapy this was continued, and if there had been no specific diet before treatment, no changes were instituted during therapy.

Two grams of combined E-CPIB and androsterone were taken daily in the form of eight 250 mg. capsules. Each capsule contained 244.5 mg. of E-CPIB and 5.5 mg. of androsterone. Cholesterol was measured by an automatic colorimetric technique based on methods previously described.[9,10] Triglycerides were determined by the method of Carlson and Wadstrom.[11] Total lipids were calculated by the technique of Folch and Van Slyke.[12]

Results

(1.) *Cholesterol:*

Table 2 lists the results of this treatment on serum cholesterol.
Statistically significant reduction in levels of cholesterol was observed.

(2.) *Triglycerides* (Table 3):

Considerable individual variation was observed in comparing levels of triglycerides before and during therapy. A statistically significant reduction in triglycerides ($P = 0.05$) for the entire group occurred.

(3.) *Total Lipids* (Table 4):

Statistically significant reduction in total lipids was observed in most patients.

Side Effects and Complications

A 36 year old male teacher (L.K.) with hypercholesterolemia and severe generalized atherosclerosis was given E-CPIB-androsterone on December 11, 1962 (Table 5). He had been treated previously with nicotinic acid without success. Leukopenia and neutropenia occurred on February 5, 1962 during the time of an infection with herpes zoster ophthalmicus. Subsequently, intermittent mild leukopenia was observed from December 11, 1962 until May 18, 1963; because of this, administration of E-CPIB-androsterone was stopped on May 18, 1963. In the ensuing months neutropenia with shift to the left became less intense. Unfortunately the patient was lost to follow-up, although the need for further study was made clear to him. He returned finally to the clinic on July 13, 1964. A bone marrow examination revealed classic changes of chronic lymphocytic leukemia. At the time of writing he has no hematologic symptoms.

Whether the ingestion of E-CPIB-androsterone in this patient played any role in the causation of leukemia cannot be answered. It is the opinion of the consulting hematologist* that the occurrence of leukopenia and neutropenia on February 5, 1962,

*Robert K. Nixon, M.D., Medical Clinic #5, Henry Ford Hospital.

Table II

CHOLESTEROL*

Patient	Pretreatment	Treatment	Decrease	Months Treated
T.W.	307	296	11	14
H.S.	408	297	111	16
A.S.	436	330	106	5
W.Z.	432	265	167	16
G.G.	376	295	81	14
L.K.	362	315	47	7
F.D.	342	279	63	16
S.S.	447	395	52	16
F.F.	350	313	37	6
M.H.	245	238	7	8
Q.B.	273	250	23	11
P.Z.	249	215	34	16
A.S.	273	297	(+24)	10
C.J.	335	266	69	10
J.F.	312	305	7	16
E.F.	327	248	79	3
R.S.	290	294	(+4)	7
D.T.	320	234	86	4
J.H.	305	275	30	9
D.D.	333	279	54	9
L.B.	300	280	20	10
R.F.	265	295	(+30)	10
L.S.	252	265	(+13)	16
K.M.	256	263	(+7)	13

Average Decrease = 42

Significance of Decrease P = 0.001

*All values are means of multiple measurements taken monthly.
(Normal value is 140-280 mg. per cent.)

Table III

TRIGLYCERIDES*

Patient	Pretreatment	Treatment	Decrease	Months Treated
T.W.	241	460	(+219)	14
H.S.	308	214	94	16
A.S.	738	439	299	5
W.Z.	1025	204	821	16
G.G.	66	96	(+30)	14
L.K.	67	73	(+6)	7
F.D.	100	83	17	16
S.S.	53	148	(+95)	16
F.F.	74	80	(+6)	6
M.H.	126	76	50	8
Q.B.	178	154	24	11
P.Z.	264	113	151	16
A.S.	185	171	14	10
C.J.	138	105	33	10
J.F.	124	67	57	16
E.F.	220	137	83	3
R.S.	152	154	(+2)	7
D.T.	386	94	192	4
J.H.	142	137	5	9
D.D.	173	138	35	9
L.B.	128	96	32	10
R.F.	252	202	50	10
L.S.	1015	620	395	16
K.M.	479	283	196	13

Average Decrease = 91

Significance of Decrease $P = 0.05$

*All values are means of multiple measurements taken monthly.
(Normal value is 40-120 mg. per cent.)

Table IV

TOTAL LIPIDS*

Patient	Pretreatment	Treatment	Decrease	Months Treated
T.W.	1765	1352	413	14
H.S.	1466	1038	428	16
A.S.	2316	1517	799	5
W.Z.	3979	1389	(2590)**	16
G.G.	867	831	36	14
L.K.	908	767	141	7
F.D.	953	869	84	16
S.S.	1249	1153	96	16
F.F.	841	867	(+26)	6
M.H.	796	670	126	8
Q.B.	840	791	49	11
P.Z.	988	652	336	16
A.S.	929	948	(+19)	10
C.J.	799	762	37	10
J.F.	914	923	(+9)	16
E.F.	1218	755	463	3
R.S.	968	867	101	7
D.T.	1238	845	393	4
J.H.	909	806	103	9
D.D.	1036	870	166	9
L.B.	964	791	173	10
R.F.	1030	1009	21	10
L.S.	1630	1615	15	16
K.M.	1195	1003	192	13

Average Decrease = 179

Significance of Decrease P = 0.001

*All values are means of multiple measurements taken monthly. (Normal value is up to 850 mg. per cent.)

**Omitted from calculations of average, and of statistical significance.

TABLE 5

PATIENT L.K.

Year	1960	1961	1962			1963								1964
Date	3-22	11-10	2-5	2-9	12-11	1-14	2-11	3-13	4-17	5-18	6-6	7-3	9-6	7-13
WBC/Cubic Millimeter	7150	8150	3300	7850	4600	17000	2600	5500	3400	5000	5400			
Differential Bands										26	12	5	1	
Neutrophils			45	70						38	35	40	31	
Eosinophils			2	1						1	4	2	1	
Lymphocytes			53	25						32	48	38	63	
Monocytes				4						2	1	4	2	
Leukocytoid Lymphs												11	2	
Toxicity										+2	+2	+2	+1	
Bone Marrow														Chronic Lymphocytic Leukemia
Medications		Nicotinic Acid 3-6 gm. daily				CPIB + Androsterone 2 gm. daily								

together with the presence of herpes zoster, indicates a strong likelihood that the blood dyscrasia was present, undetected, at that time. Nevertheless, categorical statements excluding or asserting a cause and effect relationship are impossible. It should be noted that granulocytopenia has been attributed to E-CPIB-androsterone in one patient.[13] In the remaining twenty-three cases of this series, monthly examinations and smears of the blood revealed no significant changes of leukopenia or neutropenia.

Headache was a relatively frequent side-effect, and in one patient was sufficiently severe to require cessation of therapy. In this patient the headache was reproduced with the administration of the drug. In those three patients in whom significant headache occurred simple therapeutic measures with analgesics were sufficient to control the symptoms. Pyrosis was obeserved in four patients but was obviated by instructions to take the medication after meals. Nightmares, and in other patients vivid dreams, were a curious and rather common side-effect, but did not necessitate that the drug be stopped. As has been pointed out elsewhere, although there is definite potentiation of oral anticoagulant therapy in these patients, this caused no significant complications.[14]

Ancillary Tests

Control measurements of leukocytes, SGOT, and alkaline phosphatase were made in all patients prior to treatment and monthly thereafter. In selected cases, uric acid, serum protein electrophoresis, and bromsulphalein dye retention were determined as well. Starting in June of 1963, smears of the peripheral blood were made at monthly intervals in all patients.

A temporary mild rise in SGOT was observed in one patient; it was accompanied by an intensification of chronic angina pectoris and by electrocardiographic changes compatible with myocardial ischemia. Tests of liver function made concomitantly were normal. It is presumed that the increase in SGOT did not reflect hepatotoxicity from the drug.

All other laboratory tests in all patients were normal, or did not deviate significantly from previous levels.

Discussion

These results demonstrate that during the administration of E-CPIB-androsterone lower levels of blood fats were observed in most patients of this group. The compound was most effective in patients with marked elevation of lipids and was less so in those with mild to moderate elevations. Continuation of the study over a period of fourteen months has shown no tendency for the level of blood fats to return to pretreatment levels in those patients in whom a satisfactory response has occurred.

This confirms the conclusions derived from previous studies[6,7,13] concerning the potential benefits from this compound. Hellman[8] suggests that E-CPIB alone may be effective as the combination of E-CPIB and androsterone. Further comparative clinical trials of these drugs obviously are necessary to determine their possible role singly and in combination.

As was pointed out, whether or not a cause and effect relationship existed between the administration of this medication and the subsequent appearance of chronic lymphocytic leukemia in one patient cannot be determined. Careful clinical observation of patients, together with review of pertinent parameters of their hemapoietic function is necessary in those receiving this drug.

Conclusions

A combination of E-CPIB-androsterone caused reduction in blood lipid levels in most of a group of twenty-four patients. Chronic lymphocytic leukemia was detected in one patient subsequent to the administration of this drug, but leukopenia and neutropenia had been present at least on one occasion prior to its administration. Whether any relationship exists between the administration of this drug and the blood dyscrasia is unknown. Close observation of all patients receiving this medication is necessary for the determination of its eventual role as a hypolipemic medication.

Mr. David C. Harrison of Ayerst Laboratories, New York City, performed valuable statistical analyses.

Geraldine Fritz, Patricia Miller, Glenda Rouland, Marilyn Jankowiak, and Sonya Lipnick provided technical assistance.

REFERENCES

1. Albrink, M. J.: Rationale for treatment of hyperglyceridemia. (Editorial) Ann. Intern. Med., 59:581-584, Oct. 1963.
2. Moses, C.: Atherosclerosis; mechanisms as a guide to prevention. Chap. 12, p. 192-202, Phila., Lea and Febiger, 1963.
3. Thorp, J. M., and Waring, W. S.: Modification of metabolism and distribution of lipids by ethyl chlorophenoxyisobutyrate, Nature (Lond) 194:948-949, June 9, 1962.
4. Bernstein, J. G.: Effect of thermal environment on morphology of thyroid and adrenal cortical glands in albino rat, Endocrinology, 28:985-998, June 1941.
5. Hellman, L., et al: Thyroid-androgen interrelations and the hypocholesteremic effect of androsterone, J. Clin. Endocr., 19:936-948, Aug. 1959.
6. Thorp, J. M., Experimental evaluation of an orally active combination of androsterone with ethyl chorophenoxyisobutyrate, Lancet 1:1323-1326, June 23, 1962.
7. Oliver, M. F.: Reduction of serum-lipid and uric-acid levels by an orally active androsterone, Lancet 1:1321-1323, June 23, 1962.
8. Hellman, L., et al: Reduction of cholesterol and lipids in man by ethyl p-chlorophenoxyisobutyrate, Ann. Intern. Med., 59:477-494, Oct. 1963.
9. Zlatkis, A., Zak, B., and Boyle, A. J.: New method for direct determination of serum cholesterol, J. Lab. & Clin. Med., 41:486-492, March 1953.
10. Leffler, H. H., Estimation of cholesterol in serum, Am. J. Clin. Path., 31:310-313, April, 1959.
11. Carlson, L. A., and Wadström, L. B.: Determination of glycerides in blood serum., Clin. Chim. Acta, (Amst). 4:197-205, Mar. 1959.
12. Folch, J., and Van Slyke, D. D.: Preparation of blood lipid extracts free from nonlipid extractives, Proc. Soc. Exper. Biol. & Med., 41:514-515, June, 1939.
13. Prout, B. J., and Edwards, E. A.: Agranulocytosis during administration of "Atromid". Brit. Med. J., 2:543-544, Aug. 31, 1963.
14. Oliver, M. F., et al: Effect of atromid and ethyl chlorophenoxyisobutyrate on anticoagulant requirements, Lancet 1:143-144, Jan. 19, 1963.