The Effects of Sitosterol, Nicotinic Acid and Triparanol on Fat Tolerance

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DURING recent times, much attention has been focused on hypercholesterolemia as an important factor in the genesis of atherosclerosis, especially of the coronary arteries.[1-8] On the basis of such a concept, the decrease of the various blood lipid fractions is now commonly advised.

Certain inconsistencies in the relationship between hyperlipemia and atherosclerosis do exist, however, and these have stimulated an inquiry into more precise methods of studying fat metabolism. Among them is the radioactive fat tolerance test wherein the blood radioactivity levels are measured over a twenty-four hour period following the ingestion of a test meal containing a tracer dose of radioactive iodinated triolein in a diluent of 1 ml./kg. of peanut oil. Results obtained in a group of 100 normal subjects have demonstrated that the maximum postprandial blood radioactivity value is less than 15 per cent, and the twenty-four hour level less than 5 per cent of the ingested radioactivity. In patients with proved coronary disease, on the other hand, levels have been higher than normal, the results being much more consistently abnormal than the cholesterol or any other of the serum lipids.[9-14] Accordingly, therapy directed to the correction of this abnormality appears to us to be a more rational approach than one directed toward the reduction of the hypercholesterolemia alone. We have, therefore, been interested in studying the effects of prolonged administration of several of the currently recommended hypocholesterol agents on fat tolerance as well as their ability to lower the blood cholesterol.

MATERIAL AND METHODS

Thirty patients were selected for study. Each had a blood cholesterol level in excess of 275 mg. per 100 ml. and, in addition, a certain number had positive evidences of coronary artery disease as manifested by a history of a previous myocardial infarction. In every case a radioactive fat tolerance test had been performed previously and had demonstrated an abnormal response according to our criteria.[15]

An equal number of subjects was treated with sitosterol, nicotinic acid and triparanol in accordance with the recommended doses.[16-18] Each patient received the medication for a four to six month period. Cholesterol determinations were made at monthly intervals. A repeat radioactive fat tolerance test was performed at the end of the treatment period.

RESULTS

Each of the agents used demonstrated varying degrees of effectiveness in lowering the cholesterol level (Table 1, Fig. 1, 2 and 3). Seven patients who received sitosterol showed a decrease (1 to 42 per cent). The average for the entire group was minus 3.7 per cent. In each of the patients treated with nicotinic acid there was a fall in the blood cholesterol level (1 to 36 per cent), the average being 12.6 per cent. In nine of the ten patients

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TABLE I

Effects of Treatment with Sitosterol, Nicotinic Acid and Triparanol on Cholesterol Levels and Radioactive Fat Tolerance

Patient	Cholesterol (mg./100 ml.)			Radioactive Fat Tolerance (% Blood Radioactivity)			
	Before Treatment	After Treatment	Per Cent Change	Before Treatment (max. 24 hr.)		After Treatment (max. 24 hr.)	
S-1	349	310	−11	(18.2)	(7.1)	(16.0)	(5.1)
S-2	365	340	−7	(16.7)	(9.2)	(15.4)	(11.2)
S-3	320	310	−3	(21.3)	(5.0)	(18.7)	(5.3)
S-4	439	370	−16	(15.4)	(7.2)	(16.4)	(6.6)
S-5	309	400	+29	(21.3)	(11.6)	(24.2)	(10.7)
S-6	304	350	+15	14.2	(7.1)	(15.6)	(6.8)
S-7	350	345	−1	11.7	(10.3)	14.2	(8.7)
S-8	310	310	...	(19.0)	(9.2)	(16.7)	(8.0)
S-9	455	450	−1	12.7	(5.3)	14.0	(6.0)
S-10	362	210	−42	(15.2)	(7.0)	(17.0)	(8.0)
N-1	322	290	−7	11.3	(8.2)	14.3	(5.8)
N-2	308	282	−7	(15.9)	(6.0)	14.2	(7.1)
N-3	296	276	−7	(21.3)	(11.2)	(22.4)	(14.3)
N-4	289	285	−1	10.6	(6.2)	14.3	(5.8)
N-5	374	302	−19	12.6	(5.3)	13.4	(6.1)
N-6	390	250	−36	(19.0)	(7.5)	(19.1)	(5.8)
N-7	362	298	−18	(16.3)	(5.0)	14.1	(5.4)
N-8	418	380	−9	12.2	(6.0)	13.1	(5.2)
N-9	372	320	−14	13.9	(6.2)	14.9	(5.8)
N-10	302	278	−8	(17.3)	(9.1)	(15.2)	(9.0)
T-1	362	302	−17	(16.2)	(5.8)	(17.8)	(7.1)
T-2	440	270	−39	(17.5)	(8.0)	(16.0)	(7.0)
T-3	292	267	−8	13.9	(7.2)	(15.1)	(7.0)
T-4	298	278	−7	(21.2)	(7.9)	(18.7)	(6.1)
T-5	372	338	−9	(23.1)	(6.8)	(17.1)	(5.4)
T-6	312	280	−10	14.3	(5.2)	(15.1)	(5.1)
T-7	306	312	+2	(15.3)	(7.2)	(16.1)	(5.0)
T-8	390	290	−26	(18.1)	(5.8)	(16.2)	(6.1)
T-9	400	192	−52	(17.0)	(15.0)	12.9	(11.2)
T-10	320	300	−6	14.0	(6.1)	13.7	(3.7)

NOTE: S = patients treated with sitosterol, N = patients treated with nicotinic acid, T = patients treated with triparanol. Figures in parentheses indicate abnormal values.

given triparanol there was also a lowering of the hypercholesterolemia (6 to 52 per cent), the average being 17.2 per cent. The reduction in cholesterol levels, however, was not accompanied by any significant improvement in the radioactive fat tolerance except in one case (T-10).

COMMENTS

Despite considerable evidence to the contrary, the current concept motivating the treatment of atherosclerosis holds that when this condition is accompanied by hypercholesterolemia, treatment should be directed toward the return of this lipid fraction to normal levels. This view has been extended to include even those persons with elevated cholesterol levels who do not have overt evidences of atherosclerosis.

The implication exists that when this lipid fraction abnormality is controlled, the speed of development of the atherosclerotic process will be materially retarded. Since it is known that cholesterol is only a single expression of fat metabolism, it would appear an oversimplification to judge corrective measures on the basis of this one factor.

The basic premise of the present study is that the determination of the cholesterol level, or any other single constituent such as

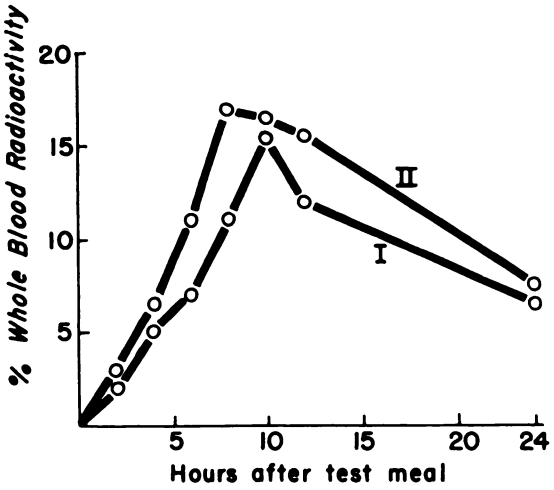

FIG. 1. Patient S-10. Results of radioactive fat tolerance tests before (I, cholesterol = 362 mg.) and after (II, cholesterol = 210 mg.) four months' treatment with sitosterol.

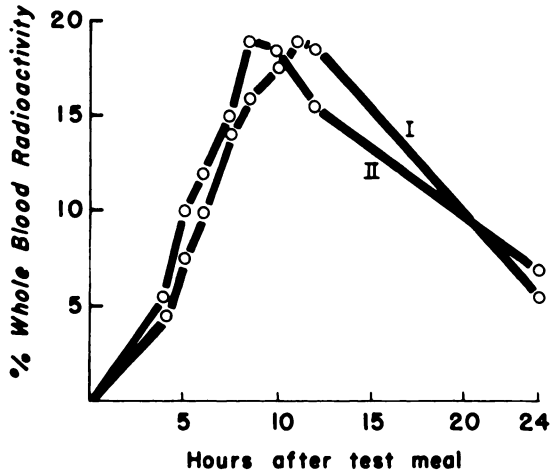

FIG. 2. Patient N-6. Results of radioactive fat tolerance tests before (I, cholesterol = 390 mg.) and after (II, cholesterol = 250 mg.) four months' treatment with nicotinic acid.

the triglycerides, lipoproteins or unesterified fatty acids, is indeed a poor reflection of the total metabolic error responsible for atherosclerosis. In the search for a more adequate agent to detect lipid dysfunction, the radioactive fat tolerance study has emerged as a sensitive device for this purpose. We have found its results to be more consistently abnormal in persons with diseases known to be related to fat metabolic errors than any of the

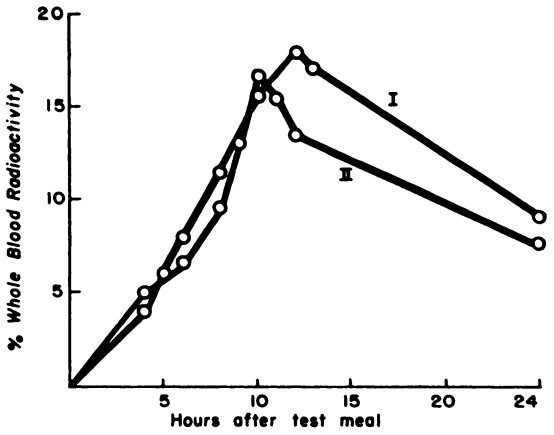

FIG. 3. Patient T-2. Results of radioactive fat tolerance tests before (I, cholesterol = 440 mg.) and after (II, cholesterol = 270 mg.) four months' treatment with triparanol.

blood lipid fractions. As such, therefore, it may represent a much more sensitive indicator of the effectiveness of various therapeutic agents in the treatment of lipid metabolic disorders than does the determination of one or more specific lipid fractions.

The present investigation strongly suggests that nicotinic acid, triparanol and sitosterol have little ability to improve fat tolerance regardless of their influence on the serum cholesterol level. It remains a moot question as to whether this proved limited effect of these agents is sufficient to influence the pathogenesis of atherosclerosis or whether a more profound influence on a fundamental mechanism such as fat tolerance must be established before real benefit is to be derived.

On the other hand, it is interesting to note that several agents, heparin[19,20] certain heparinoids[20,21] and pancreatic extracts[22] may favorably influence fat tolerance without any specific effects on the serum cholesterol.

SUMMARY

The effects of sitosterol, nicotinic acid and triparanol have been studied in a group of thirty patients with hypercholesterolemia and abnormal radioactive fat tolerance. In a certain number of cases, a decrease in the cholesterol level occurred with each drug. However, in only one instance was there any

significant improvement in the fat tolerance. It is suggested that the restricted hypocholesterol activity of these agents limits their effectiveness as atherosclerotic agents.

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