Effect of Heparin and Treburon in Postprandial Hyperlipemia. (19594)

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Since Hahn(1) demonstrated that heparin cleared alimentary hyperlipomicronemia, much work has been done to elucidate the mechanism for this action(2-4). Although it is as yet uncertain whether lipomicronemia is cleared by conglutination, dispersion, or a combined effect induced by a heparin-plasma protein complex, nevertheless the reaction is consistent and serves as a measure of heparin action upon serum lipids. The present study was concerned with the comparative effects of heparin* and Treburon† (a new synthetic heparinoid) on the physical state of serum lipids using as an index their action on alimentary lipemia. The effect on cholesterol and lipid phosphorus was also determined.

Method. The study included a total of 24 subjects. Ten patients, 2 hospitalized for rheumatic fever, 2 for myocardial infarction, 3 for pneumonia, one for bronchogenic carcinoma, one for cirrhosis, one for obesity, were given 25 g fat meals on 3 successive days. Three hours after the meal (while the lipomicronemia was reaching its maximum phase) 500 mg Treburon was given intramuscularly or sublingually, or 100 mg heparin was given intramuscularly. Medications were changed daily so that 9 of the 10 patients received all 3 medication procedures, but not in the same sequence (one patient left the hospital before heparin administration). Seven patients, 6 of whom received a 25 g fat meal, had cholesterol, cholesterol ester and lipid phosphorus determinations performed, as well as lipomicron counts before and after Treburon administration. The seventh patient of this group was fasting when these studies were undertaken. Treburon was given during the lipemic phase of digestion (6 received 500 mg intramuscularly and one 1000 mg sublingually). Three patients received similar studies using 100 mg heparin intramuscularly. Four patients served to demonstrate the variation in the normal curve of lipomicronemia after a 25 g fat meal. Each of these patients was subsequently given 250 mg Treburon intravenously 2 hours after the test meal and the effect on lipomicronemia noted prior to medication and 5, 15, and 60 minutes after medication. The lipomicronemia was determined on samples obtained from capillary blood drawn into vaccine tubing. Leaving one-third of the tube empty to prevent heat coagulation the clear end of the tube was flamed shut and the miniature test tube thus produced was centrifuged at 2,000 r.p.m. to separate serum from clot. The entire serum sample was transferred to a detergent-free, scrupulously clean glass slide by breaking the tube at the serum clot junction. A cover slip was affixed and with a drop of immersion oil on the cover slip as well as the darkfield substage examination was made using a 95 X objective and a 20 X ocular. One large square of a net micrometer inserted into the ocular was used to make the count in a single focal plane at 100 sites. To avoid subjective effects personnel doing the counts knew neither patient nor medication used. The technic was essentially that previously reported(5) except that due to the intense lipomicronemia, chylomicron index determinations (per cent of visible particles larger than 0.5 μ) could not be accurately determined. The cholesterol and cholesterol ester determinations were done according to a modification of the technic of Sperry and Schoenheimer(6). The lipid phosphorus determinations were performed according to the modified method of Youngburg and Youngburg(7).

Results. Moderate to marked reduction in lipomicronemia was produced in all 24 patients given intramuscular or intravenous heparin or Treburon (Tables I and II, and

* Heparin was furnished in generous quantities through courtesy of Upjohn Co., Kalamazoo, Mich.

† Treburon is the trademark of the sodium salt of sulfated polygalacturonic acid methyl ester methyl glycoside developed in the laboratories of Hoffmann-La Roche, Inc., Nutley, N. J., furnished by Dr. Leo A. Pirk.

TABLE I. Effect of Heparin and Treburon on Chylomicronemia. Total visible fat globules per 100 squares.

Name	Age	Intramusc. Treburon (500 mg) 3 hr p.c.	3½ hr p.c.	4 hr p.c.	Intramusc. Heparin (100 mg) 3 hr p.c.	3½ hr p.c.	4 hr p.c.	Sublingual Treburon (500 mg) 3 hr p.c.	3½ hr p.c.	4 hr p.c.
C.R.	59	520	340	200	730	360	380	570	630	710
S.M.	75	580	110	160	650	185	205	400	680	520
J.M.*	33	760	470	600	670	230	550	690	850	610
C.S.	55	188	212	50	—	—	—	410	310	220
E.S.	53	780	760	400	1500	800	750	1080	365	305
H.H.	63	840	180	605	268	116	132	1050	930	920
M.T.	54	850	124	176	—	235	300	1110	1270	820
J.G.	67	420	180	244	525	330	175	780	760	400
C.L.	78	800	410	64	850	80	80	710	500	520
E.D.	28	1160	145	110	950	180	124	790	810	880

Treburon and heparin were given 3 hr p.c. 25 g fat med.
* This patient weighed 425 lb.
p.c. stands for post cibum (after eating).

TABLE II. Effect of Heparin and Treburon on Chemical and Physical State of Serum Lipids.

Name	Age	Cholesterol Total, mg %	Cholesterol Free, mg %	Lipid phosphorus, mg %	Fat particle, 100 sq	Cholesterol Total, mg %	Cholesterol Free, mg %	Lipid phosphorus, mg %	Fat particle, 100 sq
		Before Treburon (500 mg IM)				1 hr after Treburon			
F.S.	58	220	86	—	352	205	95	—	164
R.H.	58	301	217	13.8	1180	324	186	14.2	156
J.H.	74	117	83	8.1	920	119	65	7.6	110
C.H.	67	143	55	—	990	143	55	—	188
W.M.	46	155	84	14.6	1060	142	48	13.8	290
A.S.*	45	253	175	11.3	195	256	185	11.7	196
E.D.†	28	172	70	—	450	146	67	—	930
		Before heparin (100 mg IM)				1 hr after heparin			
F.H.‡	68	167	—	7.2	69	167	—	7.2	47
J.H.	74	114	75	7.8	360	107	75	7.9	25
W.M.	46	229	55	23.2	875	217	46	22	305

Heparin and Treburon were given 3 hr p.c. 25 g fat med.
* Subsequently lipemia occurred between 3rd and 4th, not 2nd and 3rd hr.
† 1000 mg Treburon given sublingually, not intramusc.
‡ This subject was fasting.

Fig. 1). Sublingual Treburon in the doses used was ineffective in 7 of 10 patients, and significantly effective in only one. This was similar to the experience with sublingual heparin and Treburon on clotting time determinations(8). Table II demonstrates that the effect of heparin or Treburon on the physical state of postprandial serum fat emulsions is not related to any consistent change in cholesterol, cholesterol ester, or lipid phosphorus content.

Intravenous Treburon produced a clearing of postprandial lipomicronemia within 5 to 15 minutes, and this effect reached a maximum within one hour (see Fig. 1). The normal lipomicron pattern of these patients following a fat meal demonstrates that the counts were static (one) or increasing (three) between the second and third hour. These findings are in accord with those reported in previous studies(5,9).

Discussion. Moreton(10) and Necheles *et al.*(11) have felt that the postprandial lipomicronemia is more prolonged and the chylomicronemia of a greater degree in myocardial infarction patients than in normal subjects. Zinn and Griffith(5) were unable to confirm this by the technic they employed. However, if such a relationship does exist the observed effect of heparin should be beneficial. While denying any essential role in atherosclerosis to chylomicrons, Gofman and

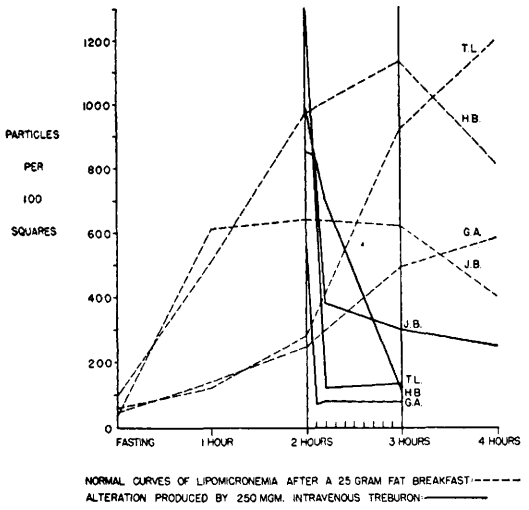

FIG. 1.

associates(12,13) have demonstrated that their atherogenic cholesterol-bearing lipoprotein molecules of the S_f 12-20 class are suppressed by heparin administration. In addition, they have presented evidence that angina pectoris was relieved for prolonged periods by administering heparin twice a week. The relationship between the chylomicron index and S_f 10-20 alterations is now under investigation in these laboratories. The significant reduction in postprandial lipomicronemia by heparin may serve as an indicator of the active principle which alters the cholesterol bearing lipoproteins Gofman has related to atherosclerosis. The findings recorded herein indicate that Treburon affects the observed physical state of serum lipids in a manner identical with heparin, and suggests that it may be substituted for heparin in clinical states where heparin has been found effective.

Conclusions. 1. Heparin or Treburon given intramuscularly were equally effective in producing a sharp fall in alimentary lipomicronemia within 30 to 60 minutes. 2. The alterations noted in serum fat emulsions were not related to changes in cholesterol, its fractions, or lipid phosphorus. These chemical determinations were not significantly influenced by either heparin or Treburon. 3. Treburon given intravenously produced a sharp drop in the lipid particle count within 5 to 15 minutes and this was maximal within one hour of injection. 4. Treburon given sublingually was ineffective.

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