The Heparin-Like Action of Treburon in Abolishing Alimentary Lipemia in Normal Individuals

By Robert F. Ackerman, M.D., and D. B. Zilversmit, Ph.D.

The effectiveness of Treburon in clearing alimentary lipemia in young adults has been studied. It is shown that the optical density of plasma at 650 mμ is a satisfactory measure of “physical” lipemia. A significant difference was noted in the extent of alimentary lipemia of young males and females.

In 1943 Hahn observed that heparin would clear lipemic plasma a few minutes after its intravenous administration. However, no clearing action of heparin was apparent when heparin was mixed with plasma in vitro. This observation has been confirmed by several other groups. Apparently heparin clears lipemic plasma by altering the physical state of the blood lipids since their chemical composition is not changed.

Treburon, a synthetic material, has a heparin-like action in preventing blood clotting. Therefore, Treburon might also abolish alimentary lipemia. The following studies were undertaken to investigate the action of Treburon on alimentary lipemia in man.

METHODS

Our procedures paralleled those of Block and Barker, except that Treburon was employed instead of heparin. A fasting sample of blood was drawn and 260 cc. of 36 per cent cream was then fed to each individual. A second blood sample was drawn three hours later. From a tuberculin syringe, a measured amount of Treburon was injected intravenously at that time and 15 minutes later the third blood sample was drawn. All blood samples were oxalated and centrifuged to separate the plasma. Timing was arranged so that the turbidity of all samples was measured one hour after the last blood sample had been drawn. The turbidity of the plasma samples was determined with a Beckman Spectrophotometer by measuring the optical density at 650 mμ against a distilled water blank.

In several experiments, chylomicron counts were made on the same plasma samples employed for the turbidity measurements. Lipemic samples were diluted 1:10 or 1:20 with 20 per cent urea before a chylomicron count was made. In confirmation of the work of Marder and associates we found that urea is a more satisfactory diluent than water or saline. Optical densities, which were measured on the diluted and original samples showed a precise proportionality to the extent of dilution, even over a concentration range of 1:100.

In some of the experiments, Treburon was administered sublingually in order to determine whether this material would be active when administered by this route. The Treburon tablets required 15 to 30 minutes to dissolve, consequently, the post-Treburon specimen was drawn approximately 30 minutes after the pre-Treburon blood sample.

RESULTS

Table 1 presents our findings when varying amounts of Treburon were administered to 16 normal, healthy females and 16 normal, healthy male subjects aged 18 to 29 years. The lipemia clearing was calculated as the percentage difference between the turbidity of lipemic and cleared samples. Block and Barker subtracted the optical density of the fasting sample from the other two before they calculated the percentage clearing. We did not use the fasting sample as a blank, however, because several of the fasting samples of the male subjects showed an appreciable optical density due to postabsorptive lipemia. Consequently, the
cleared samples sometimes showed lower optical densities than the fasting samples, a situation which would imply more than 100 per cent clearing action of the drug.

Treburon administered intravenously to young males and females in doses of 15 mg. or above showed a consistent lipemia clearing action. Below this dosage the drug showed a clearing effect in a smaller proportion of the individuals. Experiments carried out on 15

Treburon administered by this route has little or no activity in clearing lipemia.

In table 2 the optical densities and chylomicron counts of the fasting, lipemic, and cleared plasma samples of nine subjects are compared. In order to show the close agreement obtained by these two methods of measurement, the values are expressed in arbitrary units in a manner such that the lipemic samples show optical densities and chylomycin counts of 100.

**Table 1.—The Lipemia Clearing Action of Treburon in Normal Males and Females**

<table>
<thead>
<tr>
<th>Males</th>
<th>Treb. mg.</th>
<th>Optical Density</th>
<th>Clearing %*</th>
<th>Females</th>
<th>Treb. mg.</th>
<th>Optical Density</th>
<th>Clearing %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. L.</td>
<td>25</td>
<td>.091 .062 .137</td>
<td>78</td>
<td>B. S.</td>
<td>15</td>
<td>.067 .596 .259</td>
<td>57</td>
</tr>
<tr>
<td>J. T.</td>
<td>25</td>
<td>.066 .322 .676</td>
<td>49</td>
<td>J. S.</td>
<td>15</td>
<td>.075 .558 .286</td>
<td>47</td>
</tr>
<tr>
<td>C. Y.</td>
<td>25</td>
<td>.107 .853 .190</td>
<td>78</td>
<td>M. W.</td>
<td>15</td>
<td>.074 .252 .213</td>
<td>15</td>
</tr>
<tr>
<td>T. N.</td>
<td>25</td>
<td>.036 .751 .187</td>
<td>74</td>
<td>M. L.</td>
<td>12</td>
<td>.072 .407 .245</td>
<td>40</td>
</tr>
<tr>
<td>W. S.</td>
<td>15</td>
<td>.131 .498 .057</td>
<td>89</td>
<td>A. W.</td>
<td>10</td>
<td>.104 .570 .208</td>
<td>63</td>
</tr>
<tr>
<td>J. S.</td>
<td>15</td>
<td>.311 .700 .249</td>
<td>64</td>
<td>A. S.</td>
<td>10</td>
<td>.115 .351 .175</td>
<td>50</td>
</tr>
<tr>
<td>A. V.</td>
<td>15</td>
<td>.072 .469 .074</td>
<td>84</td>
<td>M. G.</td>
<td>10</td>
<td>.061 .234 .272</td>
<td>16†</td>
</tr>
<tr>
<td>H. M.</td>
<td>10</td>
<td>.065 1.238 .950</td>
<td>52</td>
<td>M. G.</td>
<td>5</td>
<td>.077 .312 .124</td>
<td>60</td>
</tr>
<tr>
<td>L. B.</td>
<td>10</td>
<td>.162 .624 .512</td>
<td>18</td>
<td>M. S.</td>
<td>5</td>
<td>.073 .125 .072</td>
<td>42</td>
</tr>
<tr>
<td>H. C.</td>
<td>10</td>
<td>.092 1.500 .906</td>
<td>40</td>
<td>M. N.</td>
<td>5</td>
<td>.208 .270 .118</td>
<td>56</td>
</tr>
<tr>
<td>J. F.</td>
<td>5</td>
<td>.054 .224 .084</td>
<td>62</td>
<td>M. S.</td>
<td>3</td>
<td>.139 .574 .301</td>
<td>47</td>
</tr>
<tr>
<td>J. R.</td>
<td>5</td>
<td>.064 .581 .288</td>
<td>54</td>
<td>C. C.</td>
<td>3</td>
<td>.169 .512 —</td>
<td>Av. 32</td>
</tr>
<tr>
<td>D. H.</td>
<td>5</td>
<td>.076 1.150 .842</td>
<td>27</td>
<td>G. E.</td>
<td>0</td>
<td>.072 .289 .251</td>
<td>13</td>
</tr>
</tbody>
</table>

* % Clearing = (OD cleared plasma / OD lipemic plasma) × 100.
† Not included in average.
‡ Readings in optical density units taken directly from the spectrophotometer scale.

In nearly all instances the agreement is remarkably close. Only in the cleared sample of the second subject is there a disagreement between the results. This deviation can be ascribed to the presence of hemolysis which contributed to the optical density of the sample.

**Discussion**

Inspection of table 1 reveals that the results obtained with Treburon are very similar to those reported by others using heparin. Whether or not the lipemia clearing activities of Treburon and heparin exist in the same

older hospitalized female patients showed entirely similar results. In 13 of these patients, doses of Treburon ranging from 15 to 150 mg. produced more than 30 per cent clearing. In two additional patients, saline was injected instead of Treburon. In both patients the degree of lipemia of the third sample was greater than that of the second one.

Treburon was administered sublingually in 500 or 1000 mg. quantities to seven hospitalized female patients. In four patients the lipemia increased, while three showed only 15 to 20 per cent clearing. It is thus evident that Trebu-
ratio as their effectiveness as anticoagulants cannot be stated with certainty at this time.

Our results indicate that young males develop a significantly greater degree of lipemia after ingestion of the test meal than do young females.* Such a difference was also noted by Block and Barker,† but not by Schwartz and co-workers.‡ If this tendency toward a lesser
degree of alimentary lipemia in women can be confirmed, one might speculate whether this observation could explain the lower incidence of atherosclerosis in women before the menopause. The close parallelism between chylomicron counts and optical densities of fasting, lipemic and cleared plasma makes the latter measure-
ment the method of choice for the quantitation of "physical" lipemias. Pigmentation of the plasma will interfere with the measurement of lipemia by light transmission, but the simplicity and time saving aspects of the method as compared with the counting of chylomicrons are so great that an occasional error due to severe hemolysis is of no great disadvantage. To avoid this possible error, Marder and co-workers§ have recommended the use of the nephelometer for the measurement of lipemia. Their data indicate, however, that the chylomicron counts and nephelometer readings are only related in a semiquantitative way. It is possible that nephelometer readings will give a useful measure of opalescence, but as a substitute for chylomicron counts the measurement of optical density appears to be the method of choice.

**SUMMARY**

1. Following the oral administration of a measured amount of cream, the intravenous injection of Treburon clears lipemic plasma. The smallest amount of Treburon with consistent action in this respect lies between 15 and 25 mg.

2. The sublingual administration of Treburon produces no definite clearing of lipemic plasma.

3. Chylomicron counts and plasma turbidities, as determined by optical densities, are proportional. Therefore, the determination of the plasma turbidity appears to be the simplest substitute for chylomicron counts.

4. After ingestion of cream, young women develop less lipemia than young men.

**ACKNOWLEDGMENTS**

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**SUMARIO ESPAÑOL**

La efectividad del Treburon en la prevención de lipemia alimenticia en adultos jóvenes ha sido estudiada. Se demuestra que la densidad óptica del plasma a 650 μm es una medida satisfactoria de lipemia física. Una diferencia
significativa se notó en el grado de lipemia alimenticia entre el adulto joven varón y la hembra.

REFERENCES


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