THE EFFECT OF HEPARIN-FREE DIALYSIS ON ABNORMAL LIPID METABOLISM IN PATIENTS ON REGULAR DIALYSIS TREATMENT

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Summary

To elucidate the contributory role of heparin to abnormal lipid metabolism in patients on regular haemodialysis (RDT), six week haemodialysis without heparin was performed using gabexate mesilate in combination with low dose aspirin. Total cholesterol and β-lipoprotein were significantly increased at the fourth week after the start of the study. No significant changes were observed in high density lipoprotein cholesterol, phospholipid, triglyceride, lipoprotein phenotype and post heparin lipolytic activity. Routine dose heparin in RDT might have a favourable effect on abnormal lipid metabolism by inducing post heparin lipolytic activity in circulating blood, not by reducing the lipid removing activity in peripheral tissues.

Introduction

The effect of haemodialysis on abnormal lipid metabolism has hitherto been controversial. As contributing factors to this abnormality, heparin as anticoagulant, dialysate glucose and acetate have been considered. However, studies on the role of glucose and acetate revealed that both had negligible effect on the abnormality [1,2]. On the other hand, although heparin induces lipolytic activity in circulating blood, its effect on lipid metabolism in RDT has not been sufficiently evaluated because of the difficulty in performing haemodialysis without heparin. Matsui et al [3] reported the possibility of haemodialysis without heparin using gabexate mesilate, a synthetic proteinase inhibitor. In their study, almost all the changes of lipids before and after a single haemodialysis procedure seemed to be caused by heparin, because lipid changes were not observed in haemodialysis without heparin. They included post-dialysis elevation of non-esterified fatty acid, high density lipoprotein cholesterol (HDL-C), plasma lipolytic activity, decrease in triglyceride (TG) and change of lipoprotein electrophoretic pattern. To elucidate the influence of repeatedly administered heparin on lipid metabolism in RDT for a longer period, we performed haemodialysis without heparin for six weeks.
Materials and methods

Eight patients on RDT were studied. Patient profile is shown in Table I. All cases had been administered multivitamins and aluminium hydroxide gel. Lipid-lowering drugs or androgenic drugs were excluded. No patients had diabetes mellitus or liver disease which might modify lipid metabolism. Lipoprotein phenotypes were determined according to WHO standards.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Cause of renal failure</th>
<th>Duration of dialysis (months)</th>
<th>Total cholesterol (mg/100 ml)</th>
<th>Triglyceride (mg/100 ml)</th>
<th>Lipoprotein phenotype</th>
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<tr>
<td>1</td>
<td>57</td>
<td>F</td>
<td>CGN</td>
<td>5</td>
<td>211</td>
<td>250</td>
<td>IV</td>
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<td>2</td>
<td>55</td>
<td>F</td>
<td>CGN</td>
<td>15</td>
<td>135</td>
<td>117</td>
<td>normal</td>
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<tr>
<td>3</td>
<td>63</td>
<td>F</td>
<td>CGN</td>
<td>7</td>
<td>137</td>
<td>55</td>
<td>normal</td>
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<tr>
<td>4</td>
<td>38</td>
<td>M</td>
<td>CGN</td>
<td>48</td>
<td>182</td>
<td>238</td>
<td>normal</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>F</td>
<td>PCK</td>
<td>42</td>
<td>191</td>
<td>161</td>
<td>normal</td>
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<tr>
<td>6</td>
<td>31</td>
<td>M</td>
<td>CGN</td>
<td>36</td>
<td>182</td>
<td>241</td>
<td>IV</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>F</td>
<td>CGN</td>
<td>49</td>
<td>144</td>
<td>201</td>
<td>IV</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>M</td>
<td>CGN</td>
<td>62</td>
<td>232</td>
<td>265</td>
<td>IIb</td>
</tr>
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</table>

CGN : chronic glomerulonephritis
PCK : polycystic kidney

Haemodialysis was performed with hollow fibre kidneys using dialysate which contained 200mg/100ml glucose and 37mEq/L acetate. Haemodialysis with heparin was performed by continuous infusion of heparin at 20U/kg body weight/hr. Haemodialysis without heparin was performed with infusion of gabezate mesilate at 1,200 to 1,800mg/hr. If intradialyser clotting was frequently observed, 0.2 to 0.3g aspirin was administered orally the night before haemodialysis.

Haemodialysis without heparin was performed for six weeks, followed by haemodialysis with heparin for the next six weeks as control period. Various blood parameters as to lipid metabolism were checked every other week after twelve hours’ fasting. Total protein, serum GOT, blood urea nitrogen, creatinine, haemoglobin and platelet count were checked at the start and the end of haemodialysis without heparin. Change in lipid metabolism was evaluated by total cholesterol (TCH) (enzyme method), HDL-C (heparin and Ca precipitation method), TG (enzyme method), phospholipid (PL) (Hoeflmayr-Fried method [4]), β-lipoprotein (immune laser nephelometry), agarose gel lipoprotein electrophoresis and post heparin lipolytic activity (PHLA). PHLA was assessed in heparinised plasma 10 minutes after intravenous injection of heparin 10U/kg body weight by the method of Schottz et al [5]. Statistical analysis was done by paired t-test.

Results

No significant changes were observed in total protein, serum GOT, blood urea
TABLE II. The effect of six-week haemodialysis with gabexate mesilate on routine laboratory tests

<table>
<thead>
<tr>
<th></th>
<th>Total protein (g/100ml)</th>
<th>Serum urea nitrogen (mg/100ml)</th>
<th>Creatinine (mg/100ml)</th>
<th>Haemoglobin (g/100ml)</th>
<th>Platelet count (x 10^4)</th>
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</thead>
<tbody>
<tr>
<td>Before</td>
<td>6.8 ± 0.2</td>
<td>19 ± 6</td>
<td>75 ± 4</td>
<td>1.0 ± 0.7</td>
<td>7.1 ± 0.8</td>
</tr>
<tr>
<td>After</td>
<td>7.1 ± 0.2</td>
<td>20 ± 8</td>
<td>80 ± 5</td>
<td>1.5 ± 1.0</td>
<td>7.0 ± 0.9</td>
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</tbody>
</table>

n = 8  
* : mean ± SEM  
all not significant

TABLE III. The effect of haemodialysis with or without heparin on lipid patterns in patients on regular haemodialysis

<table>
<thead>
<tr>
<th></th>
<th>with heparin</th>
<th>without heparin</th>
<th>with heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>2 w</td>
<td>4 w</td>
</tr>
<tr>
<td>Total cholesterol (mg/100ml)</td>
<td>177 ± 15*</td>
<td>191 ± 18</td>
<td>195 ± 18*</td>
</tr>
<tr>
<td>HDL cholesterol (mg/100ml)</td>
<td>35 ± 3</td>
<td>37 ± 5</td>
<td>35 ± 7</td>
</tr>
<tr>
<td>Phospholipid (mg/100ml)</td>
<td>171 ± 9</td>
<td>161 ± 17</td>
<td>179 ± 14</td>
</tr>
<tr>
<td>Triglyceride (mg/100ml)</td>
<td>131 ± 26</td>
<td>177 ± 31</td>
<td>183 ± 25</td>
</tr>
<tr>
<td>β-lipoprotein (mg/100ml)</td>
<td>447 ± 43</td>
<td>471 ± 47</td>
<td>522 ± 53</td>
</tr>
<tr>
<td>Postheparin lipolytic activity (nEq FFA/ml/hr)</td>
<td>1067 ± 100</td>
<td>1133 ± 127</td>
<td>1115 ± 151</td>
</tr>
</tbody>
</table>

n = 8  
*: mean ± SEM  
*: P < 0.05 vs pre value

nitrogen, creatinine, haemoglobin and platelet count by haemodialysis without heparin (Table II).

As shown in Table III, TCH and β-lipoprotein were significantly increased at the fourth week after initiation of haemodialysis without heparin. HDL-C, TG and PL did not show significant changes. PHLA was low before the start of haemodialysis without heparin and remained at the same level throughout the study.

Lipoprotein phenotype by electrophoresis did not change in any case on haemodialysis without heparin. Reinstitution of heparin did not cause any significant changes in any parameters observed. The variation of phenotypes in patients on RDT might have been induced by heparin. In this regard, modified results
were anticipated by haemodialysis without heparin. But, this study revealed no such changes, suggesting that the contribution of heparin to abnormal lipid metabolism is a limited one. The role of uraemia itself seems to be much more important.

Discussion

Since abnormal lipid metabolism is found from the early stage of chronic renal failure [6], and haemodialysis cannot essentially improve this abnormality [7], abnormal lipid metabolism observed in chronic uraemics including those on RDT is considered to be due to the reduction of functioning nephron rather than to uraemic waste products. In RDT, the effect of repeatedly administered heparin may be contributory. As reported by Matsui et al [3], heparin-induced lipolytic activity decreased TG by 30% of predialysis level. Lipoprotein electrophoretic pattern is also known to be modified by heparin-induced lipolytic activity. According to Wade [8], it takes about 24hr for lipoprotein electrophoretic pattern to return to that of predialysis.

Furthermore, heparin-induced lipolytic activity is considered to accelerate the transport of cholesterol from very low density lipoprotein (VLDL) to high density lipoprotein (HDL) through breakdown of VLDL [9]. We confirmed that HDL-C was increased by haemodialysis with heparin, but did not change significantly by haemodialysis without heparin. Therefore, it was considered that the effect of heparin on lipid metabolism in RDT is worth studying. Previous reports on the effect of heparin on lipid metabolism in RDT failed to find conclusive evidence because of the difficulty of haemodialysis without heparin.

Cabexate mesilate is confirmed not to influence lipid metabolism. Aspirin affects the cholesterol level when administered in dosage as large as 5.0g/day [10]. Since the dosage used in this study was within 0.3g/per alternate day, its influence is negligible. Furthermore, no routine laboratory examinations were changed by haemodialysis without heparin. Accordingly, our method which compared six weeks haemodialysis without heparin with a following period of haemodialysis with heparin, is at present a proper and reliable one to study lipid metabolism in RDT.

We studied eight patients of different lipoprotein phenotypes: type II B (1), type IV (3) and normal (4). An increase was observed in TCH and β-lipoprotein by withdrawal of heparin. The difference between before and the fourth week after the initiation of haemodialysis without heparin was significant in both parameters. But they did not decrease significantly after reinstitution of haemodialysis with heparin. Since β-lipoprotein contains pre-β-lipoprotein to some extent, elevation of β-lipoprotein may be due to the accumulation of pre-β-lipoprotein caused by withdrawal of heparin which induces lipolytic activity in circulating blood. The elevation of cholesterol may be the associated phenomenon.

PHLA consists of two main lipases; hepatic TG lipase and lipoprotein lipase (LPL). The former eliminates chylomicron remnant and the latter removes chylomicron and VLDL from circulating blood [10]. Therefore, PHLA is regarded as one of the indicators of lipid removing activity in circulating blood. According
to recent papers which measured hepatic TG lipase and LPL immunologically and/or by ion exchange column chromatography, both were reduced in chronic uraemics [11,12]. In this study, we checked PHLA because heparin induces both of them, in order to evaluate the effect of heparin on lipid metabolism in RDT. Since PHLA was not changed significantly throughout both study periods of haemodialysis with and without heparin, heparin is not a major contributing factor in PHLA reduction in RDT.

The fluctuation of TG over a wide range with no significant change in spite of the significant changes of TCH and β-lipoprotein may be attributed to the existence of chyomicron, confirmed by lipoprotein electrophoresis in blood samples after overnight fasting. In this study, we observed chyomicron frequently in lipoprotein electrophoresis. Overnight fasting might not have been enough to evaluate fasting triglyceride levels in RDT because of the remarkably reduced lipid-removing activity in peripheral tissue.

In conclusion, the routine dose of heparin during haemodialysis may have a favourable effect on abnormal lipid metabolism in RDT by removing cholesterol from circulating blood through induction of lipolytic activity without reducing the lipid removing activity in peripheral tissues. Abnormal lipid metabolism in uraemic patients on RDT is a reflection of the influence of neither acetate nor glucose in the dialysate, nor heparin. True contributing factors seem to exist in chronic renal failure itself.

Acknowledgments

The authors would like to express their thanks to Ono Pharmaceutical Co Ltd for offering gabexate mesilate.

References

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Open Discussion

CHAN (London) I would like to congratulate you for being able to dialyse without heparin. We have used prostacyclin in dialysis but have not been able to reduce the heparin dose below 4000 units for six hours dialysis. Did you come across any difficulties at all using this anticoagulant?

NAKAGAWA The gabexate mesilate is very rapidly inactivated, so we sometimes observed clotting. In such cases as Matsui said, we used the administration of 0.3gm aspirin for the fortnight before dialysis.

CHAN The hyperlipaemics and the normal lipaemics behave completely differently. So did you measure the post heparin lipaemia before the patients are put on heparin-free dialysis?

NAKAGAWA Yes, we should have done this study but did not have enough patients and the groups were not separated.