The Effect of Essential Amino Acid Administration on Nitrogen Metabolism during Dialysis

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It is well known that uraemic patients lose amino acids during peritoneal and haemodialysis (Berlyne et al., 1967; Ginn et al., 1968; Guylassy et al., 1968; Rubini & Gordon, 1968; Young & Parsons, 1969). This may contribute to the development of protein depletion with hypo‐proteinaemia and muscle wasting known to occur in such patients. It is of particular interest that reduced concentrations of the essential amino acids have been found in plasma from uraemic patients maintained on intermittent dialysis (Young & Parsons, 1969).

In the present study we have explored the possibility of counteracting the loss of amino acids during dialysis by administration of the eight essential amino acids with or without histidine. There is evidence that histidine behaves as an essential amino acid in uraemia (Bergström et al., 1970; Fürst et al., 1971).

MATERIAL AND METHODS

Chronic uraemic patients treated with haemodialysis 2‐3 times per week (Travenol Ultraflo 140 5‐6 hours) or with peritoneal dialysis (24 hours) 1‐2 times per week were studied. The eight essential amino acids (EAA) (2.2g N) in some cases together with histidine (0.45g N) were administered intravenously during the last 4 hours of dialysis or orally as tablets spread out over the entire dialysis. Only half the dose of EAA and histidine was given in two cases. To prevent acidosis the basic amino acids, lysine and histidine were included as the acetates instead of as the chlorides.*

Dialyses without amino acid administration served as controls. The losses of total N, urea‐N and α‐amino‐N in pooled dialysate were determined. The loss of individual amino acids during dialyses with and without amino

*The solutions and tablets were kindly provided by AB ASTRA, Södertälje, Sweden
acid administration was studied in two patients, one being on haemodialysis and the other one on peritoneal dialysis.

In two patients maintained on intermittent peritoneal dialysis and receiving a controlled nitrogen-poor diet (2.7 g N/day) (Führst et al., 1969) between dialyses, complete nitrogen balances were made during two consecutive weeks, one period without extra amino acid supply and one with daily supplementation of the 8 amino acids (2.2 g/day). In one subject the amino acids were given intravenously, and in the other orally as tablets. The nitrogen balance was corrected for changes in total body urea (total body water volume - TBW x urea-N concentration) according to Schloerb (1966). TBW was determined with tritiated water. α-amino-N was determined according to Sobel et al (1957); total nitrogen by the Kjeldahl method; urea-N by the method of Chaney & Marbach (1962), and free amino acids according to Spackmann et al (1958) using the lithium method. The balance technique used has previously been reported (Führst et al., 1967).

The amino acid compositions, in proportions according to Rose (1949), of the tablets and solution used are shown in Table I.

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>g</th>
<th>g N</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Phenylalanine</td>
<td>3.3</td>
<td>0.28</td>
</tr>
<tr>
<td>L-Isoleucine</td>
<td>2.1</td>
<td>0.22</td>
</tr>
<tr>
<td>L-Leucine</td>
<td>3.3</td>
<td>0.35</td>
</tr>
<tr>
<td>L-Lysine</td>
<td>2.4</td>
<td>0.46</td>
</tr>
<tr>
<td>L-Methionine</td>
<td>3.3</td>
<td>0.31</td>
</tr>
<tr>
<td>L-Threonine</td>
<td>1.5</td>
<td>0.18</td>
</tr>
<tr>
<td>L-Thryptophan</td>
<td>0.75</td>
<td>0.11</td>
</tr>
<tr>
<td>L-Valine</td>
<td>2.4</td>
<td>0.29</td>
</tr>
<tr>
<td>L-Histidine</td>
<td>1.65</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Total 20.7 2.65

Acetate 18 mmol

RESULTS
The loss of total-N, urea-N and α-amino-N in the dialysate during peritoneal dialyses with and without the administration of amino acids is shown in Table II.

There was a higher mean loss of α-amino-N during dialyses with amino
Table II. Loss of nitrogen in dialysate during peritoneal dialysis

<table>
<thead>
<tr>
<th></th>
<th>No E.A.A. adm.</th>
<th>E.A.A. adm. x)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean</td>
</tr>
<tr>
<td>Total-N</td>
<td>10</td>
<td>23.38±2.199</td>
</tr>
<tr>
<td>Urea-N</td>
<td>11</td>
<td>9.40±0.760</td>
</tr>
<tr>
<td>(\alpha)-amino-N</td>
<td>10</td>
<td>0.89±0.202</td>
</tr>
</tbody>
</table>

x) 2.2 g N (without histidine) or 2.65 (with histidine) corresponding to 1.91 g resp 2.07 g \(\alpha\)-amino-N.

Table III. Amino acid loss in dialysate during four peritoneal dialyses in patient RC. \(D_1\) and \(D_2\): without amino acid administration. \(D_3\) and \(D_4\) with amino acid administration

<table>
<thead>
<tr>
<th>A.A.</th>
<th>(D_1) loss mg</th>
<th>(D_2) loss mg</th>
<th>(D_3) adm. mg</th>
<th>(D_4) adm. mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val</td>
<td>29</td>
<td>32</td>
<td>2400</td>
<td>82</td>
</tr>
<tr>
<td>Met</td>
<td>15</td>
<td>19</td>
<td>3300</td>
<td>4</td>
</tr>
<tr>
<td>Ileu</td>
<td>17</td>
<td>23</td>
<td>2100</td>
<td>49</td>
</tr>
<tr>
<td>Leu</td>
<td>19</td>
<td>29</td>
<td>3300</td>
<td>66</td>
</tr>
<tr>
<td>Phe</td>
<td>12</td>
<td>17</td>
<td>3300</td>
<td>60</td>
</tr>
<tr>
<td>Lys</td>
<td>67</td>
<td>57</td>
<td>2400</td>
<td>82</td>
</tr>
<tr>
<td>His</td>
<td>191) tr.</td>
<td>1648</td>
<td>57</td>
<td>824</td>
</tr>
<tr>
<td>Thr</td>
<td>-1)</td>
<td>-1)</td>
<td>1500</td>
<td>78</td>
</tr>
<tr>
<td>Ser</td>
<td>7761)</td>
<td>3081)</td>
<td>150</td>
<td>122</td>
</tr>
<tr>
<td>Pro</td>
<td>405</td>
<td>231</td>
<td>394</td>
<td>437</td>
</tr>
<tr>
<td>Gly</td>
<td>472</td>
<td>305</td>
<td>481</td>
<td>614</td>
</tr>
<tr>
<td>Ala</td>
<td>376</td>
<td>487</td>
<td>432</td>
<td>4041)</td>
</tr>
<tr>
<td>Cys</td>
<td>tr.</td>
<td>tr.</td>
<td>140</td>
<td>168</td>
</tr>
<tr>
<td>Tyr</td>
<td>8</td>
<td>tr.</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>Arg</td>
<td>941)</td>
<td>25</td>
<td>238</td>
<td>164</td>
</tr>
<tr>
<td>Asp</td>
<td>tr.</td>
<td>4</td>
<td>tr.</td>
<td>99</td>
</tr>
</tbody>
</table>

1) Incomplete separation.

x) Essential amino acids.

acid supply than when no amino acids were given (p <0.01). The difference (0.8g N) was smaller than the extra amount of \(\alpha\)-amino-N supplied as amino acids with or without histidine (1.91-2.07g N). No significant differences in mean losses of total-N and urea-N were observed.
Table IV. Amino acid loss in dialysate during two haemodialyses (ultraflow 140) in patient AS. D₁ without amino acid administration. D₂ with amino acid administration.

<table>
<thead>
<tr>
<th>A.A.</th>
<th>D₁ loss mg</th>
<th>D₁ adm. mg</th>
<th>D₂ loss mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val</td>
<td>234</td>
<td>1200</td>
<td>440</td>
</tr>
<tr>
<td>Met</td>
<td>49</td>
<td>1650</td>
<td>250</td>
</tr>
<tr>
<td>Ileu</td>
<td>67</td>
<td>1050</td>
<td>200</td>
</tr>
<tr>
<td>Leu</td>
<td>243</td>
<td>1650</td>
<td>340</td>
</tr>
<tr>
<td>Phe</td>
<td>70</td>
<td>1650</td>
<td>380</td>
</tr>
<tr>
<td>Lys</td>
<td>327</td>
<td>1200</td>
<td>220</td>
</tr>
<tr>
<td>His</td>
<td>70</td>
<td>824</td>
<td>220</td>
</tr>
<tr>
<td>Thr</td>
<td>7821³</td>
<td>750</td>
<td>260</td>
</tr>
<tr>
<td>Ser</td>
<td>7821³</td>
<td></td>
<td>220</td>
</tr>
<tr>
<td>Pro</td>
<td>470</td>
<td></td>
<td>600</td>
</tr>
<tr>
<td>Gly</td>
<td>257</td>
<td></td>
<td>290</td>
</tr>
<tr>
<td>Ala</td>
<td>378</td>
<td></td>
<td>480</td>
</tr>
<tr>
<td>Cys</td>
<td>70</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>Tyr</td>
<td>tr.</td>
<td></td>
<td>187</td>
</tr>
<tr>
<td>Arg</td>
<td>60</td>
<td></td>
<td>220</td>
</tr>
<tr>
<td>Asp</td>
<td>24</td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>

1) Incomplete separation.
x Essential amino acids.

Figure 1. Nitrogen balance in two uraemic patients treated with peritoneal dialysis once a week. White bars: nitrogen administered; the first period by food (2.7g N/day) and the second period with the addition of EAA (2.2g N/day) daily. Black bars: nitrogen balance corrected for changes in total body urea-N. I.V. = intravenous administration; P.O. = oral administration; P.D. = peritoneal dialysis (24 hours)
The losses of individual amino acids during four peritoneal dialyses in one patient are shown in Table III. A small increase in the losses of EAA occurred when these amino acids were administered. However, these losses were negligible compared with the amounts supplied (< 10%). Of the non-essential amino acids determined, cystine, arginine and tyrosine were lost in slightly increased quantities.

Similar results were obtained during haemodialyses with and without amino acid administration (Table IV). The losses of amino acids were, however, higher than during peritoneal dialyses, 15-30% of the dose of EAA administered being recovered in the dialysate.

In the two balance studies made (Figure 1) the daily administration of the eight EAA (2.2 g/day) improved the corrected nitrogen balance considerably between dialyses without any evidence of increased urea accumulation.

**DISCUSSION**

The difference in the loss of \( \alpha \)-amino-N during dialyses with and without administration of amino acids was much smaller than the amount of \( \alpha \)-amino-N supplied in the form of amino acids. This indicates that a considerable part of these amino acids was retained.

The results of the studies in which individual amino acids were determined in the dialysate also indicated that only a small part of the amino acids infused was lost as free amino acids. Earlier studies on the incorporation of \( ^{15} \)N (administered as \( ^{15} \)N urea) into plasma and muscle protein indicate that dialysis treatment enhances the synthesis of plasma and muscle protein from non-protein nitrogenous precursors (Fürst et al., 1970). It would thus seem probable that at least part of the administered amino acids that are retained during dialyses are used in protein synthesis. The results of the balance studies indicate that daily supply of EAA between the dialyses improves the nitrogen balance considerably without excessive urea formation. These results are in agreement with findings in non-dialysed patients maintained on a protein-poor diet, who may be brought into positive nitrogen balance by administration of EAA (Giordano, 1963; Giovannetti & Maggiore, 1964; Josephson et al., 1970).

In conclusion it would appear that supply of EAA to uraemic patients on intermittent dialysis is of value, since it improves the nitrogen balance and counteracts the loss of amino acids during dialysis.

**ACKNOWLEDGMENT**

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REFERENCES

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OPEN DISCUSSION

F PARSONS (Leeds): Thank you very much, I enjoyed your paper. Could you move a little bit further: I think we all know that in chronic renal failure, when the creatinine clearance falls below 15 ml/min (and this would include all patients on regular dialysis), the essential amino acid level in the plasma is below normal and in all probability the total amino acid nitrogen is elevated. I am not too sure whether you are right in drawing the conclusion that it is the loss during dialysis that you are correcting and that this is the beneficial factor. I wonder whether you have got any more information on the individual amino acids present in the plasma, and whether you can show that the essential amino acids rise, with a corresponding fall of the non-essential amino acids? I think what you are showing here is something very fundamental in an attempt to try and correct the known abnormality of protein balance that occurs in chronic renal failure.

NORÉE: Have I understood your question correctly — that you are interested in whether we have determined the plasma amino acids individually? Well, we have started but don’t yet have the results.
A C KENNEDY (Glasgow): Could you say a little more about the method you are recommending for administration of amino acids? I am thinking particularly of patients established on regular haemodialysis who are taking a protein intake of about 60g/day. Do you recommend that at the end of each haemodialysis they have an intravenous infusion of essential amino acids, or are you suggesting that they have oral supplements of amino acids on the days between dialyses?

NORÉE: This depends. If you have a patient whom you might call well-dialysed, and on a programme three times a week, you can give him almost a free diet and if there are no signs of muscle wasting, then it might be argued that there is no need to give him amino acids at all. But if you have a patient with a poorer nutritional state, then we would use these amino acids and give them intravenously, during the last period of dialysis, as we have shown in our paper. We think this could be of great value in such conditions when you are going to feed the patient up to a better nutritional state. So you must look at the patient too.

KENNEDY: May I comment again? Presumably patients who develop deficiency of amino acids will have that deficiency before they have obvious clinical symptoms of it. Is it necessary to give as prophylaxis supplements of amino acids to someone who is apparently well and is being dialysed efficiently? Is it necessary in such individuals to give either intravenous supplements at the time of dialysis, or additional amino acids in the foods between dialyses?

NORÉE: I think this is perhaps a different question whether you should give this prophylactically. We have not studied this for very long, but still think that if you can have a free diet this is good enough.