D.T.P.A. IN THE TREATMENT OF HAEMOSIDEROSIS IN PATIENTS ON CHRONIC HAEMODIALYSIS*


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Haemosiderosis as a complication of chronic haemodialysis has been anticipated since the inception of the treatment. Two sources of excess iron are available to these patients, one through blood transfusion and the other by transfer of iron from dialysate prepared with iron rich water. Thus far, the exact role each can play in the production of the syndrome has not been determined. In Seattle, the iron content of tap water is low, and ranged from 4.7 to 6.3 μg per 100 ml over a period of 14 hours. About one third of our patients have elevated serum iron levels.

Chelating agents are being used increasingly in the treatment of haemosiderosis in people with normal renal function (Fahey et al., 1961; Clifton et al., 1963; Fairbanks et al., 1963; Walsh et al., 1963), so the possibility of its effectiveness in people on chronic haemodialysis was investigated.

The chelate used was diethylene triamine pentacetic acid (DTPA), marketed as the trisodium salt of calcium chelate by Geigy. It has a molecular weight of 497 and therefore should be readily dialysable. It contains 20 mg of calcium per gramme and its stability constant for calcium is 10.63, whereas that for iron is 16.66.

To confirm that DTPA is dialysable C14 labeled DTPA was added to a plasma reservoir and recycled through a modified Kil dialyser against an iso-osmotic dialysate for 10 hours, a similar system to that used for our chronic haemodialysis programme. The isotope was counted by the liquid scintillation method of Bloom and Nelp (1965) with an average efficiency of 72%. The half time was approximately 45 minutes and at 8 hours the count had returned to the background level, showing that the drug is completely dialysable.

In all our other experiments unlabeled DTPA was used and the amount of iron present in the outflow dialysate was measured as the indicator of effectiveness of the drug. DTPA was administered to the patients, diluted in 200 ml 5% dextrose over a one to two hour period during dialysis, into the venous line.

Dialysate samples were collected in iron free containers over 2 hourly periods and aliquots removed for estimation of iron. The iron was recovered by wet ashing the samples with sulphuric acid and adding perchloric acid or 30% hydrogen peroxide to oxidize the carbon. The material was transferred to a volumetric flask, thioglycolic acid being added to the final rinse to confirm that all the iron had been transferred. The sample was neutralized with ammonium hydroxide using 1% paranitrophenol as an indicator and diluted to volume. The colour was developed with baphthoanthroline at pH 4.6 and an aliquot read in a Beckman D.U. spectrophotometer at 535 mμ (Trinder, 1956). Control samples of dialysate before

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chelate administration were taken and the iron content was used as the background iron. To determine the amount of iron removed by DTPA, the background level was subtracted from the total iron removed. Results are expressed as μg% or mg removed per dialysis.

An in vitro study was designed to show that DTPA did not bind iron from the dialysis system. Four grams of DTPA were added to a saline reservoir during the third to fourteenth hours of dialysis. Two-hourly samples of dialysate and saline were collected and the iron content did not appreciably alter before or during chelate administration.

**TABLE I**

*Chronic haemodialysis patients*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Months of dialysis</th>
<th>Average transfusions per month</th>
<th>Serum iron μg/100 ml</th>
<th>Iron binding capacity μg/100 ml</th>
<th>% Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS</td>
<td>44</td>
<td>3.4</td>
<td>256</td>
<td>284</td>
<td>90</td>
</tr>
<tr>
<td>DB</td>
<td>41</td>
<td>3.5</td>
<td>204</td>
<td>220</td>
<td>93</td>
</tr>
<tr>
<td>KC</td>
<td>56</td>
<td>2.14</td>
<td>212</td>
<td>234</td>
<td>91</td>
</tr>
<tr>
<td>CS</td>
<td>75</td>
<td>1.1</td>
<td>34</td>
<td>296</td>
<td>11</td>
</tr>
<tr>
<td>Normal Values</td>
<td></td>
<td>70-150</td>
<td>300</td>
<td>20-50</td>
<td></td>
</tr>
</tbody>
</table>

In the clinical experiments 4 patients on chronic dialysis were studied. Details of their transfusion requirements and iron data are shown in Table I. The first 3 patients have iron overload, and bone marrow and liver biopsies showed increased iron deposition. Both the parenchymal and Kupffer cells were involved in the liver. The fourth patient, whose iron values are low, served as control.

All patients were dialysed on the modified Kiil dialyser for 12-14 hours two or three times a week. Three patients were using a central supply, single pass dialysate system (Grimsrud *et al.*, 1964), one used a 370-litre refrigerated tank with recycling.

![Graph](attachment:graph.png)

*Fig. 1*
To determine the optimum dose and time of administration of DTPA, 3 patients received doses ranging from 0.5 to 4.0 g at varying times during dialysis. Figure 1 shows the relationship between the iron in mg removed (total iron minus background iron) during 14-hour dialyses when no chelate was given and when 4 g chelate was given. The heavy lines depict the time of administration of the DTPA. When it was all given near the beginning of dialysis, the iron level was falling by the end of dialysis. When it was given in divided doses, between the second and fourth hours, and between the sixth and eighth hours, the level was still rising so that the full effect was not obtained. Thus, to obtain the maximum removal of iron during a dialysis, the chelate should be given early.

The relationship between the total iron recovered from the dialysate and the background iron, with varying doses of DTPA, is shown in Figure 2. The background iron varies, but the iron in excess of this is related to the dose of chelate in the 2 g and 3 g range. There is little increase when 0.5 g and 1 g are used, and the difference between 3 and 4 g removal is small.

Patient D.S. received 36 g of DTPA in 4 g doses during a 3-week period and Figure 3 shows the iron removed above the background iron. An average of 27 mg of iron per dialysis was removed. Results in other patients were similar. In patient C.S., who served as a control, there was no increase in the iron content of the dialysate, supporting the theory that DTPA is only active in iron removal from the body when there is excess present (Fahey et al., 1961).

Toxic reactions which have been reported with the drug include nausea, vomiting, diarrhea, thrombocytopenia, leucopenia and skin rashes (Fahey et al., 1961). Of our 4 patients, one had an episode of vomiting when receiving 4 g of DTPA when lower doses had caused no symptoms, and one patient had marrow failure. However, the latter occurred soon after an
increase in Dilantin medication and the picture of a megaloblastic anaemia was compatible with a Dilantin-induced hypersensitivity. She recovered after the withdrawal of all drugs. Periodically during dialysis this patient had a fever up to 40°C, without any obvious cause and this has been reported in another patient receiving DTPA (Cleton et al., 1963).

Our experiments are thus far incomplete. We have shown that DTPA is easily dialysable and that it binds iron in patients with definite iron overload. We have shown the optimum time of administration during dialysis but have yet to determine whether it would be better to allow a period of equilibration after administration, before dialysis. The amount of iron we have removed is less than that claimed by others for patients with normal renal function (Fahey et al., 1961; Bannerman et al., 1962). It may well be that much of the drug is immediately dialysed out before it can bind iron. Animal experiments using C¹⁴ labeled DTPA are planned to determine this point. It is also possible that DTPA may be excreted through the gastro-intestinal tract as an alternate pathway to the renal tract. Contrary to one report (Foreman, 1960) we found that anephric rabbits show a decay in plasma radioactivity over a period of up to 96 hours after the administration of C¹⁴ DTPA and radioactivity has been detected in the bile of these animals.

Clinically the optimum dose of DTPA with the minimum toxic effects appears to be 3 g given during the second hour of dialysis. The natural history of iron overload in patients on chronic dialysis treatment is still unknown. It may or may not cause the damage seen in other forms of haemosiderosis. In some of our patients over a period of one to 3 years their marrow function has improved spontaneously, reversing the haematological evidence for iron overload. However, in those patients developing the syndrome, with average monthly blood requirements of 2 units, a total of 500 mg of iron is administered. If we could remove 27 mg of iron per dialysis with DTPA, almost half the total administered could be removed monthly. This might slow down, if not halt the progression of the syndrome of iron overload.

REFERENCES

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