THE EFFECT OF DIALYSIS ON THE ARSENIC CONTENT OF BLOOD AND MUSCLE TISSUE FROM URAEMIC PATIENTS

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Arsenic is a metalloid which is mainly known for its toxic properties. It has for several centuries been one of the most popular poisons for homicide. Arsenic compounds have also been extensively used as insecticides, pesticides, and herbicides, as well as for medical purposes.

The toxicity of arsenic depends very much on the state of oxidation. The trivalent oxide $\text{As}_3\text{O}_3$ and other trivalent compounds are highly toxic with special affinity for sulphydryl groups in the living organism. Most commercially produced arsenic compounds are trivalent. Pentavalent arsenic compounds are much less toxic than the trivalent ones. Possibly pentavalent arsenic can be reduced in vivo to the toxic trivalent form (Harvey, 1965). The opposite reaction, i.e. oxidation of the trivalent to pentavalent form has been clearly demonstrated in mammals (Peoples, 1964).

Arsenic is ubiquitous in the biosphere. All living things contain arsenic, marine invertebrates having especially large quantities. Soil, sea water, and drinking water contain varying amounts of arsenic. It is generally assumed that arsenic in the organism is in the pentavalent form (Schroeder and Balassa, 1966). In animal experiments pentavalent arsenic is cleared rapidly, mainly through the kidneys, while trivalent arsenic is partly retained (Overby and Fredrickson, 1963).

Brune et al. (1966), using neutron activation analysis, determined the concentration of 8 different elements in whole blood from normal and uraemic subjects. For most elements they did not find any consistent difference in concentration between uraemic and non-uraemic subjects. One exception was arsenic, which was found in about ten times higher concentrations in uraemic than in normal blood.

The present study was undertaken in order to determine to what extent arsenic is eliminated from blood and tissue by dialysis treatment.

Material and methods

Three normal subjects and seven patients with chronic uraemia were investigated. Four of the patients were treated twice weekly with the twin-coil artificial kidney. The other three were treated by intermittent peritoneal dialysis with 1 to 4 weeks' interval.

Arsenic was determined in whole blood and in serum by activation analysis ad modum Wester (1965). In 2 cases treated by peritoneal dialysis samples from m. quadriceps femoris were obtained by needle biopsy (Bergström, 1962). The muscle samples were dried to constant weight at 90° centigrade and analysed for arsenic content.

The activation analysis method employed has a reproducibility within ± 10% or better.

Results

Table I shows the arsenic concentration in blood from normal subjects and uraemic patients. The values in the present series which were obtained before dialysis were of the same
THE EFFECT OF DIALYSIS ON THE ARSENIC CONTENT OF BLOOD AND MUSCLE TISSUE

TABLE I

Arsenic concentration (µg/g) in whole blood from normal subjects and uraemic patients

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>S.E.</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects - whole blood</td>
<td>0.0040</td>
<td>±0.0012</td>
<td>8</td>
</tr>
<tr>
<td>Uraemic patients - whole blood</td>
<td>0.035</td>
<td>±0.010</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Present material</th>
<th>Mean</th>
<th>S.E.</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects - serum</td>
<td>0.00084, 0.0013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- whole blood</td>
<td>0.0018, 0.0022, 0.0015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uraemic patients - serum</td>
<td>0.023</td>
<td>±0.0064</td>
<td>7</td>
</tr>
<tr>
<td>- whole blood</td>
<td>0.036</td>
<td>±0.011</td>
<td>7</td>
</tr>
</tbody>
</table>

TABLE II

Arsenic concentration in blood before and after haemodialysis

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Urea-N mg/100 ml</th>
<th>Creatinine mg/100 ml</th>
<th>Arsenic µg/g serum</th>
<th>whole blood</th>
<th>blood cells</th>
<th>Muscle arsenic µg/g dry weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.L.</td>
<td>pre</td>
<td></td>
<td>69</td>
<td>14.6</td>
<td>0.014</td>
<td>0.087</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>m</td>
<td>post</td>
<td>40</td>
<td>8.2</td>
<td>0.008</td>
<td>0.073</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>S.S.</td>
<td>pre</td>
<td></td>
<td>63</td>
<td>9.6</td>
<td>0.034</td>
<td>0.029</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>m</td>
<td>post</td>
<td>39</td>
<td>6.9</td>
<td>0.019</td>
<td>0.020</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>E.E.</td>
<td>pre</td>
<td></td>
<td>92</td>
<td>12.5</td>
<td>0.012</td>
<td>0.0076</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>f</td>
<td>post</td>
<td>55</td>
<td>8.8</td>
<td>0.0029</td>
<td>0.0052</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>B.S.</td>
<td>pre</td>
<td></td>
<td>77</td>
<td>12.8</td>
<td>0.018</td>
<td>0.019</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>m</td>
<td>post</td>
<td>47</td>
<td>7.8</td>
<td>0.013</td>
<td>0.011</td>
<td>0.0074</td>
<td></td>
</tr>
</tbody>
</table>

TABLE III

Arsenic concentration in blood and muscle tissue before and during peritoneal dialysis

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Urea-N mg/100 ml</th>
<th>Creatinine mg/100 ml</th>
<th>Arsenic µg/g serum</th>
<th>whole blood</th>
<th>blood cells</th>
<th>Muscle arsenic µg/g dry weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.T.</td>
<td>pre</td>
<td></td>
<td>106</td>
<td>12.0</td>
<td>0.057</td>
<td>0.070</td>
<td>0.10</td>
<td>0.0088</td>
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<tr>
<td>45</td>
<td>f</td>
<td>24 h</td>
<td>74</td>
<td>9.3</td>
<td>0.034</td>
<td>0.066</td>
<td>0.14</td>
<td>0.0060</td>
</tr>
<tr>
<td>S.A.</td>
<td>pre</td>
<td></td>
<td>129</td>
<td>17.6</td>
<td>0.0080</td>
<td>0.017</td>
<td>0.036</td>
<td>0.040</td>
</tr>
<tr>
<td>43</td>
<td>m</td>
<td>24 h</td>
<td>88</td>
<td>12.4</td>
<td>0.0075</td>
<td>0.011</td>
<td>0.017</td>
<td>—</td>
</tr>
<tr>
<td>48 h</td>
<td>84</td>
<td>48 h</td>
<td>33</td>
<td>11.6</td>
<td>0.0018</td>
<td>0.0014</td>
<td>0.0006</td>
<td>0.040</td>
</tr>
<tr>
<td>K.A.</td>
<td>pre</td>
<td></td>
<td>33</td>
<td>6.4</td>
<td>0.024</td>
<td>0.025</td>
<td>0.028</td>
<td>—</td>
</tr>
</tbody>
</table>

order of magnitude as those earlier found by Brune et al. in uraemic patients. Serum arsenic concentrations were also higher in the uraemic patients than in the two normal controls.

The results of arsenic analyses in blood before and after haemodialysis are shown in Table II.

The serum concentration of arsenic fell considerably in all cases. The changes in whole blood were proportionally smaller in all cases but one. The concentration in the blood cells (calculated from serum and whole blood concentration, and haematocrit) decreased considerably only in one case (B.S.).
The results of arsenic analyses in connection with peritoneal dialyses are shown in Table III.

The serum concentration of arsenic decreased markedly in all cases. In two cases pronounced decreases of the arsenic concentration in the blood cells also occurred. Case S.A., who was examined both after 24 and 48 hours showed the most pronounced decrease during the second 24-hour-period. The arsenic content in muscle tissue decreased slightly in case S.T. and remained unchanged in case S.A.

Discussion

The results demonstrate that the arsenic concentration in serum decreases considerably following dialysis. This indicates that arsenic is not firmly bound to the serum proteins.

The much smaller decrease in arsenic concentration in whole blood than in serum in some of the patients indicates that arsenic is slowly dialyzed from the cells. Still, relatively big decreases in arsenic concentration in the blood cells were found in two of the patients treated by peritoneal dialysis, probably due to the longer dialysis time. The arsenic content of skeletal muscle was practically unchanged after 24 to 48 hours of peritoneal dialysis. This further indicates that intracellular arsenic is not easily dialyzable.

In all probability, the accumulation of arsenic by uraemic patients occurs as a consequence of reduced renal excretion. We do not know in which form arsenic is retained in these subjects. Neither do we know whether these high arsenic concentrations are of any pathophysiological significance, i.e. if they contribute to the uraemic syndrome.

Uraemia and chronic arsenic intoxication have several symptoms in common, e.g. anorexia, nausea, and anaemia. It is of special interest that chronic arsenic intoxication is known to cause peripheral neuritis in man. More extensive clinical and experimental studies are needed in order to elucidate whether there is a causal connection between arsenic accumulation and peripheral neuropathy in uraemic patients.

REFERENCES


DISCUSSION

The Chairman: Thank you, Dr. Bergström.

These two papers are now open for discussion.

Funck-Brentano (Paris): Je voudrais faire un bref commentaire sur la communication de M. Lindholm pour souligner, comme il l'a fait, l'importance d'ajouter aux mesures de la vitesse de conduction nerveuse une étude très soigneuse de l'électromyogramme.

En effet nous avons observé chez tous nos malades ayant subi une transplantation rénale, alors qu'ils étaient déjà atteints de polynévrite, un retour de la vitesse de conduction nerveuse vers des valeurs physiologiques après transplantation.

Mais chez tous ces malades persistaient des altérations de l'électromyogramme. Dans la majorité des cas, les images électromyographiques suggéraient une réduction du nombre des unités motrices. Deux fois, les images furent celles d'une atteinte musculaire primitive. Nous nous sommes demandés si ces images de myopathie n'étaient pas dues à l'action des très fortes doses de cortisone que recevaient ces malades. Je souhaiterais connaître l'opinion de M. Lindholm sur ce point.

Lindholm (Lund): It is well known that if you do not have uraemia and give large doses of ACTH or steroids, you will get a myopathy, and this you can find with the electromyogram, with biopsies and so on.

I think that your transplant cases with these cortisone doses and uraemia have a still greater possibility of getting such a muscle dystrophy.

Most of those patients we have with chronic uraemia have signs of motor unit loss. But the point I would like to make is that in a few cases there were no signs of motor unit loss and no spontaneous activity and I think those cases did not have any myopathy, but nevertheless the motor nerve conduction velocity was reduced. What kind of nerve involvement that is do we not know exactly, but they seem to have all their nerve fibres and all their motor units still there.

Unidentified Member: I would like to ask Dr. Lindholm if his assumption is not that the toxic substance responsible for neuropathy is NPN; and if it is true that the pores of the peritoneum are bigger than those of the cellophane, do the patients on peritoneal dialysis show a lesser degree of peripheral neuropathy?

I would like to ask the members who have a long experience with chronic peritoneal dialysis if this hypothesis is true.

Boen (Amsterdam): We have been treating two patients on chronic peritoneal dialysis as you know and both, compared with patients on haemodialysis showed less abnormalities of their nerve conduction time, and, most important, did not show motor neuropathy.

The number is too small to draw any conclusion, but recently, we have been treating one patient in Amsterdam for eight months, who is working again without help at this moment.

So I believe one should entertain the idea that maybe the peritoneal membrane has larger holes, which might be able to let larger molecular substances like polypeptides pass through, which is not possible through the cellophane membrane.

One should probably investigate the possibility of making new membranes, because the problem of neuropathy is really very important for the patients, one of the most crippling conditions which can occur on the programme.
DISCUSSION

The CHAIRMAN: Can anybody else support or refute this suggestion?

SCRIBNER (Seattle): I would in general agree with Dr. Boen’s comments relative to peritoneal dialysis and neuropathy.

At the same time however, I think that we can say with some confidence now that whatever is causing the neuropathy is, in fact, dialysable. Neuropathy in our view is clearly a sign of inadequate dialysis. We have not seen a serious case of neuropathy in our experience in over two years. The minor cases that we do see, since we are much more alert to the problem, revert immediately upon increasing the amount of dialysis. We have seen nerve conduction times returning to normal with adequate dialysis.

The CHAIRMAN: Thank you. Anybody else with experience on this point?

SHALDON (London): I think the point here is the size of the product rather than the means of removing it. I think this is very important in terms of the membrane used.

I think in 1964 we reported a patient who was totally paralysed at the start of dialysis treatment, who was walking within three months by using more intensive dialysis. In our thirty odd patients on treatment, we have none with clinical symptoms of neuropathy other than one who was paralyzed at the start of treatment and has only been on dialysis for eight weeks now.

I think this is a question not merely of duration but also of the membrane used and it would be interesting to compare the incidence of neuropathy in patients dialysed with thicker cellophane with equivalent times of dialysis.

The CHAIRMAN: Perhaps Dr. Drukker will be able to tell us something about that later on today.

Any other comments on these papers?

ROTTELLAR (Barcelona): I would like to ask the doctors that have experience with neuropathy whether you observe this neuropathy more frequently in men than women. In our experience, I did not find any case in women but I found some in men. Do you believe there is any relation with the sex function?

FUNCK-BRENTANO (Paris): Dans notre expérience, nous voyons environ trois fois plus de neuropathies sévères chez les hommes que chez les femmes. That is a fact. I do not know what it means.

SCRIBNER (Seattle): I can comment on Dr. Funck-Brentano’s observation by saying that we too see three times as many patients with neuropathy who are males but we have three times as many males on dialysis!