THE EFFECT OF HAEMODIALYSIS ON ANTIBIOTIC SERUM LEVELS IN RENAL FAILURE


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Introduction 

The route of excretion of many antibiotics is via the kidneys and accordingly in renal failure, excretion of such drugs is delayed. To avoid accumulation of the drugs to toxic levels, dosage must be smaller or less frequent and ideally serum levels should be monitored.

Some decay of serum levels does occur even in complete renal failure and is presumably due to the presence of other routes of excretion, e.g. hepatic and the biliary tract.

Treatment of renal failure by haemodialysis may affect serum levels of antibiotics, and dosage schedules may again have to be adjusted. Patients undergoing chronic intermittent haemodialysis are prone to repeated infections, particularly of the urinary tract and shunt sites, and these may require antibiotic therapy.

A study to define the effects of modern haemodialysis upon rates of excretion of four antibiotics was performed and results obtained from an in vitro system and from patients undergoing haemodialysis treatment for chronic renal failure.

METHODS

All the studies were carried out using the Birmingham pattern twin-minicoil artificial kidney (Simpson et al., 1967).

In vitro experiments

During these, a solution of each antibiotic in saline was recirculated at 150 ml/min. using a roller type flow inducer, and samples were withdrawn at regular intervals for assay.

The experiment was conducted for each antibiotic in turn, using a priming volume of 500 ml of 0.9% saline containing a concentration of 250 µg/ml ampicillin, 500 µg/ml streptomycin, 50 µg/ml tetracycline or 300 µg vancomycin.

As dialysis proceeded, samples of saline were withdrawn every 15 minutes during a 2 hour period. The specimens were then stored at 4°C pending assay.

**TABLE I**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Disease</th>
<th>Duration of treatment</th>
<th>Urinary output/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>M</td>
<td>45</td>
<td>Chronic glomerulonephritis</td>
<td>18 months</td>
<td>100 ml</td>
</tr>
<tr>
<td>WB</td>
<td>M</td>
<td>33</td>
<td>Congenital polycystic kidneys</td>
<td>21 months</td>
<td>25 ml</td>
</tr>
<tr>
<td>CR</td>
<td>F</td>
<td>27</td>
<td>Chronic pyelonephritis</td>
<td>18 months</td>
<td>200 ml</td>
</tr>
<tr>
<td>JS</td>
<td>F</td>
<td>45</td>
<td>Acute fulminating glomerulonephritis</td>
<td>12 months</td>
<td>0</td>
</tr>
</tbody>
</table>

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HAEMODIALYSIS AND ANTIBIOTIC SERUM LEVELS IN RENAL FAILURE

In vivo experiments

The patients studied consisted of two males and two females undergoing chronic intermittent haemodialysis for renal failure, on an outpatient basis.

The clinical details of these patients are given in Table I.

Thirty minutes before dialysis was due to begin each patient was given a standard dose of antibiotic intravenously, namely 1 g ampicillin, 0.5 g streptomycin, 350 mg tetracycline and 0.5 g vancomycin.

At the beginning of dialysis and every 3 hours during the first dialysis, 10 ml samples of blood were withdrawn from the arterial side of the patient-kidney circuit.

Subsequent blood samples were collected at the beginning and end of each dialysis until the levels became too low to assay; occasionally additional specimens were taken midway between dialyses. The serum was separated and stored at —20°C pending assay.

Microbiological assay

Microbiological assays of antibiotics in serum and in saline were performed by the cylinder-plate method (Grove and Randall, 1959). The organisms used for the assays were Staphylococcus aureus NCTC 6571 for tetracycline and streptomycin, Sarcina lutea NCTC 8340 for ampicillin, and spores of Bacillus cereus NCTC 8035 for vancomycin.

To allow for the protein binding of antibiotics in serum, the standard solutions for the assays were prepared in pooled normal human serum, and the patients’ samples were, when necessary, diluted in the same fluid. The standard solutions for the assay of the antibiotics in saline and dilutions of the samples were prepared in phosphate buffer of optimum pH for the particular antibiotic, namely, ampicillin pH 6.0, tetracycline pH 4.5, streptomycin pH 8.0 and vancomycin pH 4.5.

Excretion rates of antibiotics

In order to compare the decay of serum levels during dialysis with that occurring naturally in renal failure, the half-life of each drug during these periods of time was calculated from the series of values obtained in the assays by the method of least squares (Kunin and Finland, 1958) using the formula:

\[
\text{half-life} = \frac{\log 2}{m} = \frac{N \Sigma (x \log y) - \Sigma x \Sigma \log y}{N \Sigma x^2 - (\Sigma x)^2}
\]

where \( x = \) time in hours
\( y = \) concentration of antibiotic
\( N = \) number of observations

RESULTS

The concentrations of antibiotic present in the saline at 15 minute intervals during a two hour period are shown in Table II. The figures show that each of the antibiotics was removed from the system by dialysis, but at different rates compared with one another. From these figures a half-life for each antibiotic was calculated. Ampicillin was dialysed the most quickly of the four antibiotics studied, streptomycin and tetracycline rather more slowly and vancomycin much more slowly.

In vitro experiments

The serum levels and half-lives for each of the antibiotics, during and between dialyses are presented in Tables III-X.
### TABLE II

**Antibiotic concentrations during in vitro dialysis experiments**

<table>
<thead>
<tr>
<th>Time of sample</th>
<th>Ampicillin</th>
<th>Streptomycin</th>
<th>Tetracycline</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min.</td>
<td>220</td>
<td>350</td>
<td>31</td>
<td>270</td>
</tr>
<tr>
<td>30 min.</td>
<td>170</td>
<td>200</td>
<td>26</td>
<td>240</td>
</tr>
<tr>
<td>45 min.</td>
<td>58</td>
<td>110</td>
<td>19</td>
<td>210</td>
</tr>
<tr>
<td>1 hr. 0 min.</td>
<td>37</td>
<td>70</td>
<td>15.5</td>
<td>160</td>
</tr>
<tr>
<td>1 hr. 15 min.</td>
<td>28</td>
<td>46</td>
<td>11.5</td>
<td>160</td>
</tr>
<tr>
<td>1 hr. 30 min.</td>
<td>17</td>
<td>34</td>
<td>9.0</td>
<td>150</td>
</tr>
<tr>
<td>1 hr. 45 min.</td>
<td>7.7</td>
<td>30</td>
<td>6.1</td>
<td>150</td>
</tr>
<tr>
<td>2 hr. 0 min.</td>
<td>3.9</td>
<td>23</td>
<td>4.4</td>
<td>125</td>
</tr>
<tr>
<td><strong>Half-life of antibiotic</strong></td>
<td><strong>18 min.</strong></td>
<td><strong>27 min.</strong></td>
<td><strong>37 min.</strong></td>
<td><strong>101 min.</strong></td>
</tr>
</tbody>
</table>

### TABLE III

**Serum levels of ampicillin in μg/ml during dialysis**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dialysis no.</th>
<th>Time in hours</th>
<th>Half-life in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>1</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.92</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.16</td>
<td>—</td>
</tr>
<tr>
<td>WB</td>
<td>1</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.75</td>
<td>—</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>69</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>66</td>
<td>—</td>
</tr>
<tr>
<td>JS</td>
<td>1</td>
<td>86</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.41</td>
<td>—</td>
</tr>
</tbody>
</table>

### TABLE IV

**Serum levels of ampicillin in μg/ml between dialyses**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period. no.</th>
<th>Time in hours</th>
<th>Half-life in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>1</td>
<td>2.0</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.92</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.16</td>
<td>3.8</td>
</tr>
<tr>
<td>WB</td>
<td>1</td>
<td>0.035</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.06</td>
<td>3.3</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>3.6</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4.2</td>
<td>—</td>
</tr>
<tr>
<td>JS</td>
<td>1</td>
<td>1.8</td>
<td>11.2</td>
</tr>
</tbody>
</table>

### TABLE V

**Serum levels of streptomycin in μg/ml during dialysis**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time in hours</th>
<th>Half-life in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>8.8</td>
<td>41.2</td>
</tr>
<tr>
<td>WB</td>
<td>7.8</td>
<td>105</td>
</tr>
<tr>
<td>CR</td>
<td>20</td>
<td>15.2</td>
</tr>
<tr>
<td>JS</td>
<td>15.5</td>
<td>30.3</td>
</tr>
</tbody>
</table>
### TABLE VI

**Serum levels of streptomycin in µg/ml between dialyses**

<table>
<thead>
<tr>
<th>Patient</th>
<th>0</th>
<th>3</th>
<th>Time in hours</th>
<th>7</th>
<th>27</th>
<th>51</th>
<th>Half-life in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>6.6</td>
<td>5.8</td>
<td>5.6</td>
<td>4.5</td>
<td>—</td>
<td>—</td>
<td>55.2</td>
</tr>
<tr>
<td>WB</td>
<td>7.2</td>
<td>6.6</td>
<td>6.4</td>
<td>4.9</td>
<td>—</td>
<td>—</td>
<td>51.5</td>
</tr>
<tr>
<td>CR</td>
<td>11</td>
<td>—</td>
<td>—</td>
<td>5.7</td>
<td>3.2</td>
<td>—</td>
<td>28.6</td>
</tr>
<tr>
<td>JS</td>
<td>11.5</td>
<td>14.5</td>
<td>—</td>
<td>10.5</td>
<td>—</td>
<td>—</td>
<td>95.8</td>
</tr>
</tbody>
</table>

### TABLE VII

**Serum levels of tetracycline in µg/ml during dialysis**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dialysis no.</th>
<th>0</th>
<th>3</th>
<th>Time in hours</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>Half-life in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>1</td>
<td>1.4</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>60.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.90</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.68</td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td>WB</td>
<td>1</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.0</td>
<td>1.2</td>
<td>38.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.65</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.55</td>
<td>62.6</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>3.5</td>
<td>3.2</td>
<td>3.1</td>
<td>2.8</td>
<td>—</td>
<td>2.5</td>
<td>31.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
<td>57.0</td>
<td></td>
</tr>
<tr>
<td>JS</td>
<td>—</td>
<td>3.5</td>
<td>3.4</td>
<td>3.6</td>
<td>3.5</td>
<td>2.7</td>
<td>2.2</td>
<td>24.1</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE VIII

**Serum levels of tetracycline in µg/ml between dialyses**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period no.</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>27</th>
<th>51</th>
<th>57</th>
<th>81</th>
<th>Half-life in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>1</td>
<td>1.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.77</td>
<td>0.99</td>
<td>0.90</td>
<td>—</td>
<td>249</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.68</td>
<td>—</td>
<td>0.67</td>
<td>—</td>
<td>0.66</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>672</td>
</tr>
<tr>
<td>WB</td>
<td>1</td>
<td>1.2</td>
<td>1.1</td>
<td>—</td>
<td>—</td>
<td>0.73</td>
<td>0.59</td>
<td>0.65</td>
<td>—</td>
<td>59.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.55</td>
<td>—</td>
<td>0.59</td>
<td>—</td>
<td>—</td>
<td>0.41</td>
<td>—</td>
<td>0.46</td>
<td>203</td>
</tr>
<tr>
<td>CR</td>
<td>—</td>
<td>2.5</td>
<td>—</td>
<td>—</td>
<td>2.3</td>
<td>—</td>
<td>—</td>
<td>1.2</td>
<td>—</td>
<td>52.9</td>
</tr>
<tr>
<td>JS</td>
<td>—</td>
<td>2.2</td>
<td>2.4</td>
<td>—</td>
<td>1.6</td>
<td>—</td>
<td>1.1</td>
<td>—</td>
<td>—</td>
<td>52.4</td>
</tr>
</tbody>
</table>

### TABLE IX

**Serum levels of vancomycin in µg/ml during dialysis**

<table>
<thead>
<tr>
<th>Patient</th>
<th>0</th>
<th>3</th>
<th>Time in hours</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>Half-life in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>9.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>8.9</td>
<td>107</td>
</tr>
<tr>
<td>WB</td>
<td>—</td>
<td>3.9</td>
<td>4.4</td>
<td>4.7</td>
<td>4.9</td>
<td>—</td>
<td>5.5</td>
<td>—</td>
</tr>
<tr>
<td>CR</td>
<td>11</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>109</td>
</tr>
<tr>
<td>JS</td>
<td>20</td>
<td>16</td>
<td>14</td>
<td>15</td>
<td>12</td>
<td>12</td>
<td>—</td>
<td>21.4</td>
</tr>
</tbody>
</table>

### TABLE X

**Serum levels of vancomycin in µg/ml between dialyses**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period no.</th>
<th>0</th>
<th>3</th>
<th>Time in hours</th>
<th>27</th>
<th>51</th>
<th>57</th>
<th>75</th>
<th>Half-life in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>—</td>
<td>18</td>
<td>—</td>
<td>10</td>
<td>—</td>
<td>9.8</td>
<td>—</td>
<td>—</td>
<td>66.1</td>
</tr>
<tr>
<td>WB</td>
<td>—</td>
<td>5.5</td>
<td>6.2</td>
<td>6.8</td>
<td>—</td>
<td>—</td>
<td>6.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>23</td>
<td>—</td>
<td>14</td>
<td>—</td>
<td>11</td>
<td>—</td>
<td>—</td>
<td>53.9</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>6.2</td>
<td>—</td>
<td>7.0</td>
<td>—</td>
<td>126</td>
</tr>
<tr>
<td>JS</td>
<td>—</td>
<td>12</td>
<td>11</td>
<td>14</td>
<td>—</td>
<td>8.8</td>
<td>—</td>
<td>—</td>
<td>170</td>
</tr>
</tbody>
</table>
TABLE XI

Mean half-lives of antibiotics during and between dialyses

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Mean half-life in hours</th>
<th>During dialyses</th>
<th>Between dialyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>7.6</td>
<td></td>
<td>24.3</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>47.9</td>
<td></td>
<td>57.8</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>44.1</td>
<td></td>
<td>214.8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>79.1</td>
<td></td>
<td>104.0</td>
</tr>
</tbody>
</table>

Table XI is a summary of the mean half-lives for each antibiotic. No half-life for vancomycin was calculated in patient WB, because the dose was given intramuscularly instead of intravenously, and this resulted in an entirely different series of serum concentrations due to delayed absorption.

Of the four antibiotics examined, ampicillin disappeared most rapidly during renal failure, the mean half-life for all four patients being 24.3 hours. Vancomycin, on the other hand, was excreted very slowly, its half-life being approximately 8 days. Streptomycin and tetracycline were intermediate between these two extremes.

During dialysis the half-lives of all the four antibiotics were shortened, but by varying proportions. The most marked effect was upon tetracycline, the half-life of which fell by 80% to 44 hours, and on ampicillin which was reduced by 69%, but vancomycin fell by only 24% and streptomycin by 17%.

DISCUSSION

The results of the in vitro experiments are not directly comparable with those obtained in vivo, as the conditions for removal of the antibiotic differed. The volume of saline used in vitro was much smaller than the compartment of distribution in vivo, so that recirculation through the artificial kidney was quicker and dialysis of the drug correspondingly more rapid. In the body too, protein binding of the drug may also delay excretion, compared with the in vitro protein-free system. On the other hand, as compared with the human body, there were no other routes of excretion or inactivation in the closed artificial kidney system.

Nevertheless, the in vitro experiments establish that the antibiotics are in fact dialysed out by the membranes used and that, under standard conditions, ampicillin is dialysed rapidly, streptomycin and tetracycline less rapidly, and vancomycin very slowly. In the absence of any other routes of excretion, this variation must represent the actual differences in dialysance between the four drugs.

The free flow of an antibiotic across a dialysis membrane is impeded if the drug is bound to proteins, only that fraction which is unbound being dialysable. All antibiotics are in a reversible state of partial binding to the serum proteins, mainly to albumin (Lithander, 1964). The part that this phenomenon plays in the maintenance of serum levels is uncertain, but in a recent review of the significance of protein binding of antibiotics, Robinson (1967) concludes that its influence varies with the mode of excretion of the drug, as it will retard removal by glomerular filtration, but is less likely to affect tubular or biliary secretion.

Figures for the protein binding of the antibiotics used in our experiments, as taken from the published literature, are ampicillin 18% (Robinson and Sutherland, 1965), streptomycin 30% (Scholtan and Schmid, 1963), tetracycline 70% (Robinson et al., 1965) and vancomycin less than 10% (Lindholm and Murray, 1966).

The results in vivo show that during haemodialysis the rate of excretion of the four antibiotics studied is increased, but that the increase in rate is not directly related to the dialysance of each drug in a protein-free system, or directly to the protein binding of each drug. However, the importance of protein binding can only really be assessed when comparing drugs
which are otherwise alike in molecular size, metabolism and other properties, such as between
the several tetracyclines.

Previous studies of the action of haemodialysis on serum levels of antibiotics disagree
about its effect on the excretion rate.

Kunin and Atuk (1966) examined serum levels of cephaloridine in 3 patients with renal
failure. The half-life of this antibiotic was found to be 19.3 to 20.8 hours, but during haemo-
dialysis the half-life dropped to between 2.4 and 4.3 hours, varying with the type of artificial
kidney used. They noted that protein binding of cephaloridine was not significant, and
suggested that this may influence dialysis rates, particularly when compared with cephalothin,
which is more highly bound.

Conversely, Bulger et al. (1964) studied the effects of renal failure and haemodialysis on
methicillin and oxacillin blood levels, and found that oxacillin disappeared more rapidly
in spite of being the more highly protein-bound. Serum levels of both drugs showed that no
appreciable effect was made by haemodialysis on the decay curve.

Lindholm and Murray (1966) determined serial serum levels of vancomycin in patients
undergoing repeated dialyses and found that the disappearance rate was not appreciably
altered by haemodialysis and that levels above 3 μg/ml may persist for up to 21 days. As the
drug is less than 10% bound to serum proteins, it seems that protein binding is not an im-
portant factor in delaying excretion of vancomycin.

In patients with renal failure standard doses of antibiotics cannot be relied upon to produce
ordinary blood levels. Some degree of accumulation will usually occur. If in addition the
patient is being treated by intermittent haemodialysis, some antibiotics will be more rapidly
dialysed than others, producing in some instances blood levels which are well below the
therapeutic range (e.g. ampicillin). Conversely, if overdosage occurs, other antibiotics, e.g.
vancomycin and streptomycin, cannot easily be dialysed out, so that the dosage in these
situations must be decided upon by consideration of these factors.

The best way to regulate the dosage of an antibiotic in these cases is by regular assay of
the blood level whilst the dose is being gradually increased.

Summary

A study of effects of haemodialysis upon antibiotic blood levels was carried out in four
patients in chronic renal failure, and also in a comparable in vitro system.

The results demonstrate that during haemodialysis, the half-lives of all the antibiotics
used were decreased, and that different antibiotics were dialysed at different rates.

The possible clinical significance of these findings is discussed.

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