Turnover Rate of Skeletal Alkaline Phosphatase in Humans

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Two patients with Paget’s disease of bone were subjected to plasmapheresis. Alkaline phosphatase activities of serum declined sharply, but returned to pre-plasmapheresis values within eight to 10 days. The biological half-life of circulating skeletal alkaline phosphatase, as calculated from these experiments, is between 1.12 and 2.15 days.

Additional Keyphrases: enzyme activity • plasmapheresis • Paget’s disease • bone disease

Alkaline phosphatase [orthophosphoric-monoester phosphohydrolase (alkaline optimum); EC 3.1.3.1] activity in plasma is remarkably stable within a given individual over long periods of time (1, 2). Injection experiments have shown that the various circulating isoenzymes of alkaline phosphatase are removed and (or) degraded at constant, fractional rates (2, 3) and that the removal mechanism(s) are not saturable, even at relatively high enzyme activities (3). There is no evidence that the different alkaline phosphatase isoenzymes influence their own or one another’s rates of delivery into or removal from plasma, and there is no evidence of a feedback effect of any circulating alkaline phosphatase on rates of production by different tissues.

Very few studies have been published concerning the turnover of skeletal alkaline phosphatase in plasma of humans (3, 4) or other mammalian species (5). We therefore subjected two volunteers with severe Paget’s disease to three plasmapheresis procedures, to decrease drastically the alkaline phosphatase activities in their plasma. From the rates of return to pre-treatment values, we could calculate the turnover rate for skeletal alkaline phosphatase.

Materials and Methods

Two patients, one a man of age 67 and the other a woman of age 69, with widespread Paget’s disease gave informed consent to the procedure, which was approved by the Ethics Committee of Sydney Hospital. Alkaline phosphatase activity in serum was measured by the automated method of Morgenstern et al. (6) with 2-amino-2-methyl-1-propanol (0.5 mol/L, pH 10.25) as a buffer. The mean pretreatment values for alkaline phosphatase in serum were 3090 U/L for the male patient and 3160 U/L for the woman.

All of the circulating enzyme behaved like skeletal material during heat denaturation (6).

Plasmapheresis was carried out by Dr. J. Isbister of Royal North Shore Hospital, Sydney, who used an Aminco continuous-flow cell separator (American Instrument Co., Silver Spring, MD 20910) for 2 h (twice for the woman and once for the man) with a plasma exchange of 2 L on each occasion. The replacement fluid was human albumin in Hartmann’s solution, 50 g/L. Blood for estimation of alkaline phosphatase activity in serum was taken before and within 2 h after the end of the procedure and then daily until pre-plasmapheresis values were reached. We determined the enzyme’s activity in each sample in the same assay.

Turnover rates were calculated according to the formula

\[ r = k \left( C_t - \frac{C_0}{e^{kt}} \right) \left( 1 - \frac{1}{e^{kt}} \right) \]

where \( r \) = rate of influx into the circulation (in U/day), \( C_t \) = enzyme activity in U/L at time \( t \) (in days), \( C_0 \) = enzyme activity at zero time, and \( k \) is the fractional rate of efflux per day (as a fraction of the enzyme activity at any time). In this formula it is assumed that, in the unperturbed state, the rates of influx and efflux are equal (1).

Results

The patients tolerated the procedure well and reported no improvement or deterioration in their symptoms. Alkaline phosphatase values for both patients after three plasmaphereses are shown graphically in Figure 1; the actual data for one patient are listed in Table 1.

The rate constants for the degradation of skeletal alkaline phosphatase, calculated from these three experiments, were 0.276 and 0.314 for the woman and 0.463 for the man. Between 28 and 46% of circulating skeletal alkaline phosphatase was removed from the circulation of these patients each day, so that the biological half-life for this enzyme is between 1.12 and 2.15 days.

Fig. 1. Alkaline phosphatase activity in serum after three plasmapheresis procedures

Patient 1, 69-year-old woman; patient 2, 87-year-old man. From these values we calculated a biological half-life of one to two days for this isoenzyme.

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1 There is good evidence (7) that results are similar whether serum or plasma samples are used for alkaline phosphatase measurements.

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Table 1. Serum Alkaline Phosphatase Activity before and after a Single Plasmapheresis Procedure in a 69-Year-Old Woman with Paget's Disease

<table>
<thead>
<tr>
<th>Day *</th>
<th>Alk. Phos. activity U/L</th>
<th>Day</th>
<th>Alk. Phos. activity U/L</th>
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<td>−7</td>
<td>3300</td>
<td>+5</td>
<td>2634</td>
</tr>
<tr>
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<td>3242</td>
<td>+6</td>
<td>2605</td>
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<tr>
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</tr>
<tr>
<td>+3</td>
<td>2258</td>
<td>+15</td>
<td>3242</td>
</tr>
</tbody>
</table>

* Before (−) or after (+) plasmapheresis.

Measurements of alkaline phosphatase in serum were also made before and after hip replacement in two pagetic patients who were not receiving any anti-pagetic therapy. In each case, massive blood transfusions were given at the time of operation, with a dramatic decrease in alkaline phosphatase activity (9). However, the return to pre-transfusion values was much slower than that seen after plasmapheresis. In one case, pre-transfusional values had not been reached three months after operation.

Discussion

To our knowledge, there are only three previous studies concerning the turnover of human skeletal alkaline phosphatase in humans. Clubb et al. (3) injected pagetic serum into two human subjects and calculated a biological half-life of 40 h. Walton et al. (4), who measured alkaline phosphatase in the serum of one patient after the amputation of a pagetic tibia, calculated a biological half-life of 1.7 days (40.8 h). Whyte et al. (unpublished) infused pagetic serum into a 6-month-old girl with hypophosphatasia and obtained a half-life of 47.6 h for the infused alkaline phosphatase (personal communication).

We are unable to account for the difference between the changes in alkaline phosphatase activity in serum after plasmapheresis (Figure 1) and those after massive transfusions (9). Kanis et al. (10) suggested that pagetic tissue may have been removed during hip replacement, leading to a long-term decrease in alkaline phosphatase activity. However, in one of our two surgical patients, the femoral head showed no evidence of Paget's disease.

Our conjecture is that the long-term decrease in alkaline phosphatase activity after hip replacement and massive blood transfusions may be due to the removal of some substance or substances during the operation or to the administration of some substance or substances during anaesthesia, surgery, or transfusion. Whether or not this phenomenon has potential clinical implications, it makes "exchange" transfusions during surgical operations unsuitable for the calculation of turnover rates of skeletal alkaline phosphatase.

On the other hand, the turnover rates we calculated from the plasmapheresis experiments are similar to those obtained by Clubb et al. (3), by Walton et al. (4), and by Whyte et al. (unpublished). A biological half-life of one to two days for skeletal alkaline phosphatase ranks this enzyme between intestinal alkaline phosphatase, which has a half-life measured in minutes (11), and human placental alkaline phosphatase, with its half-life of approximately seven days (3).

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References