PHOSPHORUS KINETICS DURING HAEMODIALYSIS AND HAEMOFILTRATION

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Summary

Phosphorus excretion during haemodialysis positively correlates with the plasma inorganic phosphorus ($P_i$) concentration and the dialyser $P_i$ clearance. Therefore, by using highly efficient dialysers or haemofilters, disciplined patients may achieve a well regulated P-balance.

The plasma $P_i$ concentration time curve during haemodialysis or haemofiltration must be seen as the result of passive diffusion combined with an active mobilisation of $P_i$ from a rapidly exchangeable $P$-pool.

The plasma $P_i$ concentration hardly falls below the normal range in dialysis patients, regardless of the quantity of $P_i$ removed by haemodialysis or haemofiltration. The stability of plasma $P_i$ demonstrates the existence of a mechanism for phosphate regulation in body fluids, independent of the calcium homeostasis.

Introduction

Our investigations were originally designed to determine whether or not high efficiency dialysers could effect a significant increase in phosphate elimination, resulting in a reduced oral phosphate binder requirement. In the course of these investigations, several conspicuous peculiarities in the phosphate kinetics became apparent. Owing to their basic significance, they are reported in this paper.

Patients and methods

The following parameters were determined in dialysis patients with no residual renal excretory function:

1. The behaviour of the plasma concentrations of urea, creatinine, and inorganic phosphorus ($P_i$) during a four or eight hour haemodialysis or haemofiltration.
2. The concentration and total excretion of these metabolites in the dialysate (or haemofiltrate).
3. The clearance of these substances, whereby we distinguished between:

a) the in vivo blood clearance: \( K_{Bm} = \frac{Q_B(\text{CP}_i - \text{CP}_o)}{\text{CP}_i} + \frac{Q_F(\text{CP}_i)}{\text{CP}_i} \)

b) the blood side plasma clearance: \( K_{P,\text{blood}} = \frac{Q_B(1-H)\text{CP}_i - [Q_B(1-H) - Q_F] \text{CP}_o}{\text{CP}_i} \)

c) the dialysate side plasma clearance: \( K_{P,\text{dial}} = \frac{Q_D \text{CD}_o}{\text{CP}_i} \)

\( Q_B \) and \( Q_D \): incoming or outgoing blood flow (cm\(^3\)/min); \( \text{CD}_o \): solute concentration in the dialysate outlet flow (cm\(^3\)/min); \( Q_D \): dialysate outlet flow (cm\(^3\)/min); \( \text{CP}_i \) and \( \text{CP}_o \): plasma concentrations in the incoming or outgoing blood stream; \( Q_F \): ultrafiltrate (cm\(^3\)); \( H \): haematocrit.

The plasma concentrations of urea, creatinine, uric acid, and \( P_i \) were determined on a SMA II Technicon®, the concentrations in the dialysate or haemofiltrate on a GSA 300 Greiner®. The method of Itaya et al [1] was used with minor modifications to determine the \( P_i \) concentration in the dialysate.

Blood flow was measured by the bubble-flow method, the dialysate outflow was collected and measured.

Either a GF 180M hollow fibre or a GL 1.36 plate dialyser was used for phosphorus kinetic studies during haemodialysis; FH 303 for haemofiltration.

Results

Clearance and total excretion of urea, creatinine and \( P_i \)

The values of the in vivo blood clearance (\( K_{Bm} \)) disagree with those of the blood side and dialysate side plasma clearance considerably (Table I). The \( K_{Bm} \) is useful only in comparing the efficiencies of different dialysers. Conclusions as to the actual mass transfer during haemodialysis are not possible, however, since the \( K_{Bm} \) is influenced by haematocrit, active and passive transport of substances between plasma and erythrocyte ICF, and by changes in protein binding during passage through the dialyser. During dialyser passage, urea diffuses not only out of the plasma, but also out of the erythrocytes. This easily explains the higher \( K_{P,\text{dial}} \) compared with the \( K_{P,\text{blood}} \) values. The differences between \( K_{P,\text{dial}} \) and \( K_{P,\text{blood}} \) for creatinine and \( P_i \) undoubtedly also result from their different concentrations in plasma and erythrocyte ICF and their diffusion disequilibrium during the blood passage. Disregarding methodological error the \( K_{P,\text{dial}} \) proved best for kinetic calculations.

The total quantity of \( P_i \) excretion correlates with the plasma \( P_i \) concentration during haemodialysis or haemofiltration, and with the \( P_i \) clearance of the dialyser or the ultrafiltrate efficiency of the haemofilter (comparisons in Table I).
<table>
<thead>
<tr>
<th></th>
<th>Urea (mmol/L)</th>
<th>Creatinine (µmol/L)</th>
<th>Inorganic phosphorus (mmol/L)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>GF 180 M</td>
<td>Gl 1.36</td>
<td>HF 303</td>
</tr>
<tr>
<td>Initial concentration</td>
<td>27.47±1.93</td>
<td>25.26±4.24</td>
<td>32.50±8.52</td>
</tr>
<tr>
<td>Removal (g)</td>
<td>45.5±7.84</td>
<td>31.92±9.71</td>
<td>20.44±6.44</td>
</tr>
<tr>
<td>$K_{Bm}$ (cm³/min)</td>
<td>192±3.8</td>
<td>173±4.4</td>
<td></td>
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<tr>
<td>$K_{p\text{-dial}}$ (cm³/min)</td>
<td>163±17.0</td>
<td>150±4.0</td>
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<tr>
<td>$K_{p\text{-blood}}$ (cm³/min)</td>
<td>142±10.9</td>
<td>137±29.5</td>
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</table>
Passive diffusion and active mobilisation of $P_i$ during haemodialysis and haemofiltration. Evidence for an independent $P_i$ regulatory mechanism

The decrease in concentration of a solute which is uniformly distributed throughout the total body fluid and which can diffuse from ICF to ECF with negligible resistance and thus may diffuse freely through a dialyser membrane, demonstrates first order kinetics:

$$C_t = C_0 e^{-K.T/V} = \text{(where } C_t=\text{concentration at time } t, C_0=\text{initial concentration, } T=\text{duration of haemodialysis in minutes, } K=K_p\text{-dial, and } V=\text{effective volume of solute distribution, e.g. 60 per cent of body water).}$$

Urea is undoubtedly the only substance for which these assumptions obtain. Therefore, the experimentally determined fall in urea concentration corresponds well to the calculated value (Figure 1). Creatinine and uric acid behave similarly,

![Figure 1](image)

although not identically. The behaviour of $P_i$ is different: with initial $P_i$ above normal, the concentration falls sharply within the first two hours of haemodialysis or haemofiltration (Figure 2). As soon as the normal $P_i$ range (0.8–1.4mmol/L) is reached, the concentration remains constant or varies within the normal range, regardless of haemodialysis blood flow ($Q_B = 300$ or $200\text{cm}^3/\text{min}$). Even after eight hours of haemodialysis values do not fall below the normal range, unless the patient is suffering from a wasting disease (sepsis, cachexia, etc). Theoretically, the $P_i$ concentration should be reduced to considerably lower levels after eight hours of haemodialysis and presuming constant diffusion from the ICF. If the $P_i$ level is normal before haemodialysis, it remains in the normal range in spite of continuous removal of $P_i$.
Since the clearance rates of P_i during haemofiltration are of the same order of magnitude as the $K_{p\text{-dial}}$ for dialysers of average efficiency, the P_i concentration behaves the same during haemofiltration as in haemodialysis (Figure 3).

Upon termination of haemodialysis, a rebound in P_i occurs in a regular fashion. In the first hour following a four hour haemodialysis, a relatively steep rebound is observed in all patients. It depends on the level of the initial concentration as well as on the rate of removal. After the third hour following haemodialysis, P_i continues to rise only in patients whose predialysis concentrations were above normal. In these patients, P_i values reach approximately 80 per cent of their original value after 12 hours (Figure 4).

Discussion

The behaviour of the P_i concentration during and after haemodialysis or haemofiltration cannot be explained solely on the basis of passive diffusion of P_i out of
diverse compartments. During haemodialysis or haemofiltration, the $P_i$ concentration should drop continuously, even assuming that $P_i$ is replaced by passive diffusion from a large reservoir. However no tendency to a continuous decrease
in $P_i$ concentration was observed in any patient. Similar observations have been reported by Sugisaki et al [2].

To explain the $P_i$ kinetics during haemodialysis or haemofiltration, it must be seen as the result of a combination of two processes: passive diffusion out of a fluid space somewhat larger than the ECF, and active mobilisation of $P_i$. Apparently, $P_i$ in concentrations exceeding 1.4 mmol/L represents a waste product, which diffuses freely during haemodialysis, much like urea. Active mobilisation begins when the $P_i$ value reaches the normal range. Possibly, $P_i$ is mobilised from a rapidly exchangeable phosphate pool, whose existence has long been postulated in nuclear medicine [3], but has not yet been proven.

Active $P_i$ mobilisation during haemodialysis and haemofiltration to stabilise the plasma $P_i$ in the normal range implies the existence of a regulatory mechanism for $P_i$ homeostasis. This mechanism still functions in kidney failure and is also independent of calcium homeostasis. During haemodialysis, the total and ionised calcium concentrations increase, and the secretion of parathyroid hormone often decreases. Therefore, the well-known physiological dependence of the $P_i$ concentration on calcium homeostasis plays no part in this regulatory mechanism.

The obvious tendency to protect itself from a drop in $P_i$ level below a certain value by means of an independent regulatory system poses a series of new questions. The nature of the regulatory mechanism, the capacity of the rapidly exchangeable $P$-pool, and the consequences of acute hypophosphataemia as well as chronic phosphate depletion which might be masked by normal pre- or post-dialytic $P_i$ values, are subjects which will merit future interest.

References

1. Itaya K et al. Clin Chim Acta 1966; 14: 361

Open Discussion

BAZZATO (Montre) In the last slide you postulate the removal of phosphorus from the intracellular space. Do you have any data concerning the removal using acetate or bicarbonate buffers? Mastrangelo* has shown a better reduction in plasma phosphate during bicarbonate dialysis.

POGLITSCH I heard your interesting paper but we do not have any experience with the bicarbonate or acetate dialysis to differentiate the relative efficiencies. I think that pH must have an influence on the phosphate pool but not on the principle behaviour.

VON ALBERTINI (Los Angeles) We were particularly concerned with our method, which was shown previously†, whether we would be able to remove

the same amount of phosphorus in a short time. Indeed, we have been able to achieve it and we have confirmed this independently by measurements in the dialysate effluent. The pattern of behaviour is indeed such that plasma phosphate falls initially and very often goes up again in the second half of dialysis. Studies in the first half of dialysis indicates that phosphate seems to be removed adequately.