Pro/Con debate: the calculation on calcium balance in dialysis lowers the dialysate calcium concentrations (pro part)

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Prior to the advent of calcitriol therapy, haemodialysis (HD) patients were often in negative calcium (Ca) balance between dialyses because of severely impaired Ca absorption [1] that led to the recommendation of dialysate inlet Ca concentration (CdiCa++) 3.0–3.5 mEq/L, higher than plasma concentration [2]. Over the past 25 years since the advent of calcitriol, virtually all haemodialysis patients absorbed a substantial portion of dietary and phosphate binder calcium ingested between dialyses and yet CdiCa++ 3.0 mEq/L has continued to be widely used. The total Ca absorbed between dialyses (CaAbsT) must be removed by the dialyser (JdCaT) to achieve net zero Ca mass balance over the dialysis cycle and prevent chronic Ca overload that likely contributes to the high rate of vascular calcification in haemodialysis patients [3–5]. From this perspective, it follows that the CdiCa++ prescribed should result in neutral Ca mass balance and thus total Ca removed during dialysis (JdTCa++) should equal CaAbs in accordance with

\[ J_{dt}Ca^{++} = J_{Diff}Ca^{++} + J_{Conv}Ca^{++} = Ca_{AbsT}. \] (1)

The equality in Equation (1) can only be achieved through reliable estimation of CaAbs and prescription of equivalent total Ca removal by selection of an appropriate CdiCa++.

Ca absorption

A kinetic model of Ca absorption as a function of Ca intake and calcitriol concentration [6] is depicted in Figure 1. The model was derived from a reported series of single meal studies of CaAbs over a Ca intake range 200–1250 mg and calcitriol 8–80 pg/mL [7–10], and in Figure 1 it is extrapolated to a Ca intake of 3000 mg/day that might be expected with very high doses of Ca-based phosphorus (P) binders. It can be seen in Figure 1 that modelled CaAbs conforms to a family of logarithmic curves suggesting saturation of calcitriol-dependent absorption as Ca intake increases. The absorption curves for normal levels of calcitriol (20–40 pg/mL) would be seen in normal subjects and in HD patients treated with relatively low doses of Vit D analogues—calcitriol, 0.5–0.75 µg/dialysis, and Hecterol and Zemplar, 3–5 µg/dialysis. Ca absorption was recently reported with Ca intake distributed over 3 meals per day as diet, Ca alone (1425 mg Ca), diet plus Sevelamer (1340 mg Ca) and diet plus CaCO3 (3040 mg Ca total) [11]. The amount of CaAbs was determined from measurement of daily 24-h urinary calcium excretion over 1 week in 12 healthy normal subjects. The results of this study are also plotted in Figure 1 where they can be seen to fit the curves modelled for normal calcitriol concentration perfectly out to 3000 mg/day intake and provide strong evidence for the validity of the CaAbs model. A CaAbs curve calculated from data reported by Kopple and Coburn in 1971 [1] is also plotted in Figure 1 and illustrates the striking increase in CaAbs over the past 30 years from 0 mg/day to ~200 mg/day with an intake of 1500 mg/day and low doses of Vit D3 analogues. Ca intake and absorption values calculated from Heinrich data are listed in Figure 2 where the removal required per dialysis is also calculated and shown to be quite substantial for both sevelamer (500 mg/dialysis) and CaCO3 (650 mg/dialysis).

Dialyser Ca flux

Instantaneous Ca flux (JdCa++, mEq) during dialysis is determined by (i) the ionized Ca++ concentration gradient between plasma inlet (CpiCa++) and dialysate inlet (CdiCa++) of the dialyser, i.e. (CdiCa++ - CpiCa++), mEq/L; (ii) the dialysance of Ca++ (DCa, L/min) and (iii) the product of the ultrafiltration rate (Qf) and CpiCa++. These parameters can be combined into a well-known transport equation [12]

\[ J_{d}Ca^{++} = Da(C_{di}Ca^{++} - C_{pi}Ca^{++}) \times (1 - Qf/Qe) + Qf*Qp. \] (2)
Dialysate calcium concentrations 2995

Fig. 1. A kinetic model of Ca absorption as a function of serum calcitriol and Ca intake.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Ave Diet Ca mg/day</th>
<th>Binder Ca mg/day</th>
<th>Total Ca Int mg/day</th>
<th>Urine Ca mg/day</th>
<th>Net Ca Abs mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1398</td>
<td>0</td>
<td>1424</td>
<td>186</td>
<td>185</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>1338</td>
<td>0</td>
<td>1337</td>
<td>198</td>
<td>198</td>
</tr>
<tr>
<td>CaCO₃</td>
<td>1437</td>
<td>1600</td>
<td>3037</td>
<td>267</td>
<td>263</td>
</tr>
</tbody>
</table>

* for zero Ca Balance with Placebo and Sevelamer would need to remove ~500 mg Ca/dialysis
** for zero Ca Balance with CaCO₃ would need to remove ~650 mg Ca/dialysis (expect lower absorption with CaCO₃)

Fig. 2. Summary Ca balances reported by Heinrich et al. [11]. Note that with both sevelamer and CaCO₃, there is substantial Ca absorption which would require a removal of 500–600 mg of Ca during each three times weekly haemodialysis in order to achieve neutral Ca balance.

The miscible Ca pool (MCP)

Equation (2) describes the instantaneous Ca⁺⁺ flux, but to estimate total (T) flux over the dialysis it is necessary to also predict the mean CₚCa⁺⁺ during dialysis. We have previously described the buffering of changes in CₚCa⁺⁺ during dialysis induced by diffusive removal as the amount of Ca⁺⁺ mobilized from (M+Ca) or sequestered in (M−Ca) the MCP resisting the change in CₚCa⁺⁺ [13]. It is very helpful to generalize this relationship conceptually with a buffer constant (Kₘₚ) defined as

\[ Kₘₚ = \frac{M_{Ca}}{[M_{Ca} + \Delta C_{p}Ca^{++} \cdot V_{ECW}]} \]

where \([\Delta C_{p}Ca^{++} \cdot V_{ECW}]\) is the product of total change in plasma Ca⁺⁺ during dialysis multiplied by extracellular fluid volume (V_{ECW}) estimated as 1/3 of V_{U}.

Note that Kₘₚ can vary between 1.00 (\(\Delta C_{p}Ca^{++} \cdot V_{ECW} = 0\)) and 0 (M_{Ca} = 0). We have observed an average Kₘₚ = 0.70 in calcium modelling studies to date.

Overall modelling of Ca mass balance

Panel A in Figure 3 depicts an in vivo plot of Equation (1) derived from 26 sets of serial measurements (unpublished results of ongoing studies) of C_{di}Ca⁺⁺ and C_{do}Ca⁺⁺ (every 10 min) and three serial CₚCa⁺⁺ values during 3.5-

4-h high flux dialyses at blood flow 400, dialysate flow 500 and average total ultrafiltrate 3.0 L with polysulfone (Optiflux 180, FMC) dialysers. From the regression line, it can be seen that removal of 600 mg of Ca predicts a required mean inlet Ca⁺⁺ concentration gradient of ~0.9 mEq/L.

Panel B in Figure 3 depicts the predicted change in plasma Ca⁺⁺ during dialysis, \(\Delta C_{p}Ca^{++}\), as a function of the total amount removed and Kₘₚ. Note that very little change in CₚCa⁺⁺ is predicted for J_{d}CaT ≤ 200 mg that is the region of primarily convective removal. As J_{d}Ca increases, CₚCa⁺⁺ is predicted to fall linearly with slope determined by Kₘₚ. With an average Kₘₚ of 0.70, the predicted fall in CₚCa⁺⁺ would be 0.60 mEq/L with a removal of 600 mg Ca.

What level of C_{di}Ca⁺⁺ is required to achieve neutral Ca⁺⁺ mass balance?

We recently performed a Ca kinetic modelling (CKM) survey to calculate CaAbs on 320 Fresenius Medical Care
(FMC) patients in three dialysis facilities using the most recent monthly treatment data including pre- and postdialysis $C_{pi}Ca^{++}$, serum P and UKM measurements. The kinetic analysis showed median $Ca_{ABs}$ = 150 mg/day and required removal 350 mg/dialysis (substantially less than shown in Figure 2 because of lower dietary Ca intake). We then modelled the $Ca_{di}^{++}$ which would result in neutral Ca mass balance in those patients, and the cumulative frequency distribution of the results is shown in Panel C of Figure 2. The median modelled $Ca_{di}^{++}$ was 2.2 mEq/L and ranged from 1.5 to 3.0 in individual patients as a function of $C_{pi}Ca^{++}$, $Ca_{ABs}$ and $K_{MP}$ in individual patients. The actual $Ca_{di}^{++}$ prescribed in these patients was 2.50 in 80% and 2.25 in 20%, so in many, the kinetic analysis suggested substantial positive Ca balance.

What are the potential problems with targeting neutral Ca balance?

Targeting diffusive removal of Ca during dialysis will result in some fall in $C_{pi}Ca^{++}$ as quantified above and may carry a theoretical risk of increased arrhythmias and or stimulation of increased PTH secretion during dialysis. The corrected QT interval (QTC) in the electrocardiogram has been reported to increase with $Ca_{di}^{++}<3.0$ resulting in a suggestion that $Ca_{di}^{++}<3.0$ should be avoided [14,15] even though abnormal QTC’s and arrhythmias were not observed in the studies. These two studies in fact resulted in mild hypercalcaemia with these levels of $Ca_{di}^{++}$ and the reduction of QTC observed might more appropriately be considered a side effect of hypercalcaemia. In view of the very high incidence of vascular calcification and substantial interdialytic $Ca_{ABs}$ with modern dialysis therapy, it is not rational to prescribe positive Ca balance during dialysis by using high $Ca_{di}^{++}$. It is possible that an inappropriate increase in PTH secretion might occur with regularly prescribed negative Ca balance during dialysis and require concomitant therapy with a calcimimetic agent. These theoretical issues must be evaluated in the context of the theoretical risk associated with chronic Ca and P overload with appropriate prospective studies. Finally, all studies of management of mineral metabolism in HD patients should include consideration of the effects of the total therapeutic regimen on Ca mass balance. None of the many studies of Ca-based versus non-Ca-based binders have included the standardization of prescribed $Ca_{di}^{++}$ and a dose of Vit D$_3$ analogues which have such powerful effects on Ca mass balance [16].

Conflict of interest statement. Author is a consultant at Fresenius Medical Care.

References

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