Rapid Communication

Stabilized polynuclear iron hydroxide is an efficient oral phosphate binder in uraemic patients

Olaf Hergesell and Eberhard Ritz

Department Internal Medicine, Ruperto Carola University Heidelberg, Heidelberg, Germany

Abstract

Background. There is a continuing need for non-aluminium and non-calcium-containing oral phosphate binders. A novel product, i.e. stabilized polynuclear iron hydroxide, has experimentally been shown to be an effective phosphate binder. The purpose of the study was to test the efficacy and tolerability of the compound in hyperphosphataemic patients with stable preterminal renal failure.

Methods. In an open uncontrolled study we examined a total of 13 patients with stable preterminal renal failure (median serum-creatinine 5.4 mg/dl, range 4.2–7.3 mg/dl) and hyperphosphataemia (median fasting plasma-Pi 2.2 mmol/l, range 1.95–3.0 mmol/l). Patients were given dietary advise to maintain a constant intake of phosphate and this was verified by measuring urinary Pi excretion. After 2 weeks on no oral phosphate binders, patients were given daily 3 × 2.5 g stabilized polynuclear iron hydroxide with meals for 4 weeks. In a blinded fashion plasma-Pi and urinary-Pi as well as 1,84 i-PTH, vitamin D metabolites, serum-iron and ferritin were measured in a central laboratory.

Results. Compared to baseline (no oral phosphate binders), the median per cent decrease of fasting plasma-Pi at day 14 was 20% (7.2–41%) (P < 0.001 by Wilcoxon test) and the median per cent decrease of urinary P excretion was 37% (9.6–56.6%) (P < 0.0003 by Wilcoxon test for paired differences). Ferritin levels did not differ significantly during the study. Apart from a certain laxative action and black discoloration of the faeces, no side effects were noted in this short-term study.

Conclusion. Stabilized polynuclear iron hydroxide is a promising, efficacious and well tolerated phosphate binder.

Key words: Aluminium; calcium carbonate; hyperparathyroidism; hyperphosphataemia; phosphate binder; renal failure

Introduction

There has been increasing recognition of the importance of hyperphosphataemia, not only in the genesis of hyperparathyroidism [1,2], but also as a novel risk factor for cardiac complications. Hyperphosphataemia predicts cardiac death, and is correlated to calcification of atherosclerotic plaques [3] and aortic valve calcification [4]. It is practically impossible to control hyperphosphataemia by dietary restriction of phosphate. As a result, administration of phosphate binders per os is usually required. Because of their toxicity, aluminium-containing phosphate binders should be avoided if possible [5,6]. Calcium carbonate or calcium acetate are currently the most widely used phosphate binders, but their use is limited by the development of hypercalcaemia, particularly if the patients are treated with active vitamin D metabolites and/or if bone turnover is low [7]. This dilemma has stimulated an intense search for alternative non-calcium- and non-aluminium-containing phosphate binders. Such novel products include renagel, i.e. a crosslinked poly(allylamine hydrochloride) [8,9], an iron polymaltose complex [10], or cross-linked iron dextran [11], which has been used successfully in experimental animals [12]. A further development of the latter compound, i.e. stabilized polynuclear iron hydroxide [13], chemical formula $\text{[Fe}_2\text{O}_3(\text{OH}^\text{3})_{5/3}\text{H}_2\text{O}^\text{1/m(C6H}_{10}\text{O}_5)^\text{m}]}_\text{n}$ appears to be a promising, new compound which has remarkable in vitro binding capacity for phosphate (Pi) compared to the cross-linked iron dextran.

We performed an open uncontrolled study in patients with stable preterminal renal failure to assess the effect of oral administration of this compound on plasma- and urinary-Pi.

Patients and methods

Patients

In the renal outpatient clinic in Heidelberg we approached all consecutive patients with plasma phosphate > 2.0 mmol/l and creatinine clearance < 20 ml/min. Thirteen patients were approached and all consented to participate. These were
eight males and five females, median age 61 years, range 42–74. The underlying renal diseases were: diabetic nephropathy \((n=6)\), IgA-glo-merulonephritis \((n=3)\), polycystic kidney disease \((n=1)\), reflux nephropathy \((n=1)\), membranous glomerulonephritis \((n=1)\) and chronic glomerulo-nephritis, not biopsy proven \((n=1)\). Besides the study medication, all patients received antihypertensive agents \(i.e.\) ACE-inhibitors \((n=6)\), calcium-channel blockers \((n=8)\), \(\beta\)-receptor blockers \((n=4)\), clonidin \((n=3)\), alpha-receptor blockers \((n=5)\) and diuretics, \(i.e.\) frusemide \((n=11)\), or other diuretics \((n=5)\), respectively. Two patients were on treatment with omeprazol. Aluminium- or magnesium-containing antacids had not been prescribed to any of the patients. Three patients were on treatment with calcitriol, and three with cholecalciferol. Dose or administration interval were not changed during the study period.

The study protocol had been approved by the local ethics committee. All patients gave written informed consent.

**Design**

Patients were taken off phosphate binders and advised by a dietitian how to keep their dietary phosphate intake constant. This was verified by three measurements in the 2 weeks prior to the study. Median urinary phosphate excretion was 23.5 mmol/day, range 21–34 mmol/day; median intraindividual VC 8.6%, 4.5–17.8%. After the run-in period without phosphate binders, patients were subsequently given a constant dose of \(3 \times 2.5 \text{g}\) stabilized polynuclear iron hydroxide \(\text{courtesy Vifor Company, St. Gallen, Switzerland}\) provided as a powder in preweighed sachets. The material was suspended in water and ingested together with meals. Plasma-Pi and urinary-Pi in 24-h urine collections were measured once weekly for the total duration of 4 weeks study.

**Measurements**

All measurements were performed in a central laboratory under blinded conditions. The i-PTH peptide in plasma was measured by two-site immunoradiometric assay \[14\]. \(1,25(\text{OH})_2\text{D}\) was quantitated by radioimmunoassay \[15\] and \(25(\text{OH})\text{D}\) by protein binding assay \[16\]. Plasma-Pi and urinary-Pi and urinary-Pi were measured using autoanalyser techniques. The same was true for creatinine, urine-creatinine, alkaline phosphatase, total protein, and calcium. Determination of serum-iron and serum-ferritin was carried out with standard methods.

**Statistics**

The predetermined primary end-points were the per cent decrease of (i) fasting plasma-Pi concentration and (ii) of daily urinary-Pi excretion. These differences were evaluated by Wilcoxon test for paired differences. All other measurements were regarded as descriptive and exploratory. Data which are not normally distributed are given as median and range.

**Results**

**Baseline data**

Table 1 gives the relevant parameters of calcium metabolism and renal function at the beginning of the study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Range</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-creatinine</td>
<td>5.3</td>
<td>3.8–7.9</td>
<td>0.4–1.3 mg/dl</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>17.2</td>
<td>12.3–20.1</td>
<td>90–120 ml/min</td>
</tr>
<tr>
<td>Plasma-calcium</td>
<td>2.45</td>
<td>2.01–2.62</td>
<td>2.2–2.6 mmol/l</td>
</tr>
<tr>
<td>Plasma-phosphosphate</td>
<td>2.2</td>
<td>1.95–3.0</td>
<td>0.8–1.45 mmol/l</td>
</tr>
<tr>
<td>Plasma-bicarbonate</td>
<td>18.2</td>
<td>15.8–21.1</td>
<td>22–26 mmol/l</td>
</tr>
<tr>
<td>i-PTH</td>
<td>18.3</td>
<td>6.0–56.2</td>
<td>1.2–6 mmol/l</td>
</tr>
<tr>
<td>(25(\text{OH})\text{D})</td>
<td>48</td>
<td>27–206</td>
<td>50–200 mmol/l</td>
</tr>
<tr>
<td>Plasma-ferritin</td>
<td>127</td>
<td>99–192</td>
<td>40–170 U/l</td>
</tr>
<tr>
<td>Total protein</td>
<td>67.4</td>
<td>46–81</td>
<td>65–83 g/l</td>
</tr>
<tr>
<td>Serum-ferritin</td>
<td>113</td>
<td>24–227</td>
<td>309–300(^*) \mu g/l</td>
</tr>
<tr>
<td>Serum-iron</td>
<td>423</td>
<td>365–890</td>
<td>400–1500 \mu g/l</td>
</tr>
</tbody>
</table>

Values are given as median and range. \(*\) Male; \(*\) female.

**Plasma and urinary phosphate during the study**

Figure 1 gives the individual values for per cent decrease of plasma-Pi in the 13 patients at days 14 and 28. Figure 2 gives the per cent decrease of urinary-Pi excretion rate in the individual 13 patients at days 14 and 28. The median per cent decrease between the average plasma-Pi concentration in the run-in period and the treatment period was 20% \(\text{range }7.2–41\%\). The respective figures for urinary-Pi excretion were 37% \(\text{range }9.6–56.6\%\). With one exception, potentially caused by non-compliance, the effect persisted throughout the 28-day observation period. Table 2 gives the information on plasma-Pi concentration and urinary-Pi excretion at the end of the the run-in phase and during treatment phase on day 14 and 28. The values of plasma-Pi on day 14 and 28, respectively did not differ more than by 6.7% \(\text{range }4–14\%\) and urinary-Pi by 11% \(\text{range }2–18\%\).

**Ancillary measurements**

Table 3 gives the changes of Ca, i-PTH, \(1,25(\text{OH})_2\text{D}\), \(25(\text{OH})\text{D}\), serum iron and ferritin concentrations at the end of the run-in and the end of the treatment phase \(\text{day }28\) respectively.

**Side effects**

All patients reported that the frequency of defecation had increased \(\text{from an average of one per day, range }0–3, \text{in the run-in phase to two per day, range }1–4\). Faeces turned black, reflecting the increased iron content. The average volume of water consumed by dissolving the contents of the sachets was 75 ml per sachet \(\text{range }50–100\text{ ml}\). Patients did not report any side effects, apart from increased frequency of defecation.

**Discussion**

The results of this uncontrolled open pilot study are encouraging. It was designed to evaluate efficacy and
Stabilized polynuclear iron hydroxide is an efficient oral phosphate binder in uraemic patients.

Fig. 1. Per cent decrease of plasma phosphate in 13 patients with stable preterminal renal failure at days 14 and 28, respectively.

Fig. 2. Per cent decrease of urinary phosphate excretion in 13 patients with stable preterminal renal failure at days 14 and 28, respectively.

Table 2. Plasma-phosphate concentration and urinary phosphate excretion at the end of the run-in phase (day 0) and at days 14 and 28 of the study

<table>
<thead>
<tr>
<th></th>
<th>End of run-in period (day 0)</th>
<th>Treatment phase (day 14)</th>
<th>Treatment phase (day 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary-phosphate</td>
<td>27.0 (21–34)</td>
<td>17 (12–27)</td>
<td>16.3 (15–24.3)</td>
</tr>
<tr>
<td>(mmol/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma-phosphate</td>
<td>2.2 (1.95–3.0)</td>
<td>1.7 (1.3–2.03)</td>
<td>1.7 (1.02–2.3)</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values as median and range.

tolerability of a novel phosphate binder. The results document a consistent decrease of plasma-Pi and a reduction of urinary-Pi in all of the 13 hyperphosphatemic patients with stable preterminal renal failure, at least initially. The delayed increase in one of 13 patients raises the suspicion of non-compliance. The tolerability of the compound was excellent (this was confirmed by the investigators who also ingested the compound over the same period). Nevertheless modifications of the preparation to further reduce the amount of water required for suspending the compound are desirable.

The dose of $3 \times 2.5$ g/day that we had selected based on pilot studies in animals failed to produce normophosphataemia in most patients. Nevertheless, the average 37% decrease of urinary-Pi excretion indicates that a substantial amount of phosphate had been bound in the intestine. Presumably a somewhat higher dose is required to achieve normophosphataemia.

In principle this insoluble polynuclear iron(III)-hydroxide acts by iron–phosphate complex formation [13]. Further product information is given in the patent application text [13].

In brief, the *in vitro* binding capacity is $0.0063$ mmolP/mg Fe at a bath concentration of
Table 3. 1,25(OH)\(_2\)-D, 25(OH)-D, i-PTH, plasma-calcium, serum-ferritin and serum-iron values at the end of the run-in phase and at days 14 and 28 of the study

<table>
<thead>
<tr>
<th></th>
<th>End of run-in period (day 0)</th>
<th>Treatment phase (day 14)</th>
<th>Treatment phase (day 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-calcium (mmol/l)</td>
<td>2.39 (2.01–2.6)</td>
<td>2.42 (1.97–2.51)</td>
<td>2.38 (2.02–2.54)</td>
</tr>
<tr>
<td>i-PTH (pmol/l)</td>
<td>18.3 (6.0–56.2)</td>
<td>20.5 (4.0–23)</td>
<td>19 (8.3–25)</td>
</tr>
<tr>
<td>1,25(OH)(_2)-D (pg/ml)</td>
<td>20.5 (&lt;10–51)</td>
<td>19.6 (11–14)</td>
<td>18 (10–37)</td>
</tr>
<tr>
<td>Serum-ferritin (ug/l)</td>
<td>113 (24–227)</td>
<td>110 (20–248)</td>
<td>115 (29–234)</td>
</tr>
<tr>
<td>Serum-iron (ug/l)</td>
<td>423 (365–890)</td>
<td>417 (350–935)</td>
<td>420 (349–910)</td>
</tr>
</tbody>
</table>

Values as median and range.

1 mol Fe\(^{3+}\) and 0.4 mol P. From pH 3 to 8, adsorption capacity changes by less than 3%. This is not influenced by coincubation with various concentrations of calciumacetate. Iron solubility in vitro after 5 h at a final concentration of 500 mg Fe/l at 37 °C varies between 0% (at pH 8) and 2.1% (at pH 3). In vivo absorption of iron (\(^{59}\)Fe-labelled phosphate binder) in white mice was 0.55%±0.1% in fasting and 0.46%±0.1% in fed animals. From the reduction of urinary-Pi excretion in abnormalities in renal failure.

References
7. Ritz E, Passlick-Deetjen J, Lippert J. What is the appropriate dialysate calcium concentration for the dialysis patient? *Nephrol Dial Transplant* 1996; 11 [Suppl 3]: 91–95

Acknowledgements. We thank Dr Geisser and Dr Philipp (Vifor Company, St. Gallen, Switzerland) for kindly providing the phosphate binder and information on toxicity as well as in vitro efficacy.
Stabilized polynuclear iron hydroxide is an efficient oral phosphate binder in uraemic patients


Received for publication: 11.1.99
Accepted: 15.1.99