HIGH-EFFECTIVE ALUMINIUM FREE PHOSPHATE BINDER. IN VITRO AND IN VIVO STUDIES

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Summary

For the purpose of intestinal phosphate binding we have developed aluminium free natural polymers consisting of heteropolyuronic acid charged with different cations. The in vitro experiments showed an efficacy two to three times greater than Aludrox®. During up to six months of clinical application no serious side effects have been detected, constipation ceased and serum phosphate was maintained in an acceptable range.

Introduction

Aluminium accumulation and its sequelae in chronic renal failure patients [1—4] is possibly a consequence of aluminium hydroxide medication, providing correct water preparation for dialysis is achieved. For the purpose of intestinal phosphate binding we have developed aluminium free substances which have been tested in vitro and in vivo.

Methods

The substances under investigation are natural polymers consisting of heteropolyuronides charged with calcium or a combination of calcium and iron (Fe⁺⁺ and Fe⁺⁺⁺). These natural polymers are non-toxic, licensed food additives and do not cause constipation. The substance is produced in small particles 1—2mm in size.

We have studied the capacity for phosphate removal by differently charged heteropolyuronides in vitro in Tris buffer solution under different pH conditions and compared the results with commonly available aluminium phosphate binders. Furthermore the calcium charged substance has been incubated with human duodenal juice, which has been enriched with 2g sodium phosphate imitating the phosphate load of an average meal. During the two-hour incubation period the phosphate binding capacity has been determined. Ten chronic renal failure
patients with continuous problems in controlling their serum phosphate by conventional aluminium hydroxide therapy were treated with the calcium charged substance for up to six months and four additional patients received the calcium-iron charged product for up to three months.

Results

The polymer charged with calcium or a combination of calcium and iron contains little sodium (20mg/g) or potassium (7.8mg/g). The calcium content was found to be 140–160mg/g, the iron content of the calcium-iron charged product was 40mg/g (Figure 1).

Figure 1. Mixture of the polymeric substance. Fair particles are calcium-charged, dark particles are charged with a combination of calcium and iron

In the first study 1g of the charged polymers were incubated in 200ml Tris buffered solution containing 0.4g phosphorus at 37° C (Figure 2). The calcium charged substance failed to work under acidic pH conditions (pH 2), whereas the calcium-iron charged product was capable of binding 0.05g phosphate (16% of total binding capacity) under acidic condition. Coming to neutral and alkalotic pH values, the particles swell in the presence of phosphate and the charged cations are released gradually allowing phosphate to be entrapped. The calcium charged substance was capable of binding 0.2g phosphorus (50%), whereas the calcium-iron charged product neutralised 0.29g phosphorus (72.5%)
Figure 2. Phosphate binding capacity of the calcium charged product (1) and the calcium-iron charged polymer (2) in comparison to Aludrox® (3) under different pH conditions.

Figure 3. Phosphate binding effect of 2.4g calcium charged polymer in human duodenal juice at 37°C enriched with 2g sodium phosphate over a 120 minute incubation period.
in comparison to Aludrox®, which only binds 0.095g phosphorus (23.75%) under these conditions.

For the purpose of a test procedure closer to physiological conditions we studied human duodenal juice enriched with 2g sodium phosphate. This solution was incubated with 2.4g calcium charged phosphate binder and stirred at 37°C. During the first 45 minutes a sharp decline of the phosphate concentration was noted followed by only minor changes for the rest of the incubation time. After 120 minutes phosphate concentrations were found similar to those prior to the phosphate load (Figure 3).

Ten patients suffering from end-stage renal failure on haemodialysis with elevated serum phosphate on conventional aluminium hydroxide therapy (mean dose 2.8 ± 1.8g/day) have been treated with the calcium charged polymer for up to six months (Table I). We have not detected any undesirable reactions or

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<th>TABLE I. Mean serum phosphate, serum calcium levels and dosage of calcium charged polymer in 10 chronic renal failure patients on haemodialysis over a period of six months</th>
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constipation which is a frequent problem with aluminium hydroxide therapy. With a dose of 4–7g/day serum phosphate fell from a mean of 8.5 ± 1.7mg% to 6.1 ± 1.0mg% after six months, whereas serum calcium and serum potassium did not change substantially.

Four patients were treated with the calcium-iron charged product for up to three months. Essentially similar results have been obtained so far. A conclusive comparison and evaluation will only be obtained after extended clinical studies.

Discussion

According to the EDTA Registry [5] over 90 per cent of dialysis centres regularly give aluminium containing phosphate binders to some or all of their patients. Only a few centres (16%) regularly monitor aluminium concentrations in water and dialysis fluid and in patients’ serum [5], so the question about the cause of
aluminium accumulation cannot be answered reliably at the moment. But there is consistent data [6–10] that aluminium is resorbed enterally, so its use should be abandoned if possible.

The new substances tested for their phosphate binding capacity are natural polymers consisting of heteropolyuronides and charged with calcium and iron cations. The iron containing preparation trapped phosphate under acidic pH conditions, whereas under neutral and alkalotic pH values the particles swell and dissolve in the presence of phosphate. Calcium is release gradually and calcium-phosphate is formed which partially remains in the polymeric matrix. Depending from the polymers’ calcium load and the phosphate ingestion there might be some calcium available for absorption, as serum calcium values rose in some patients. Possibly a cation exchange between calcium and sodium or potassium may take place, as we have noticed decreasing serum potassium concentration in particular cases. As far as the in vitro experiments are concerned, the phosphate binding efficacy per g substance is two to three times greater than that of Aludrox®. This polymer system can be used for controlled release of other ions (e.g. zinc, magnesium) and of water soluble drugs avoiding undesired high substance concentrations.

References

1. Alfrey AC, Mishell JM, Burks J et al. Trans ASAIO 1972; XVIII: 257
4. Druke T. Nephron 1980; 26: 207

Open Discussion

SLATOPOLSKY (St Louis, USA) I want to congratulate you on this excellent paper, there is hope that one day we will be able to get rid of aluminium. I am concerned about the values you obtain after six months’ treatment, phosphate 6mg% and calcium 2.2mmol/L, the phosphate is too high and the calcium too low. I suspect that the amount of binders you have used is too small and I strongly suggest that you increase the dose to correct the serum phosphate.

SCHNEIDER You are quite correct, the amount of phosphate binder has to be increased. The decreasing serum calcium may not be a real effect as the number of patients are small.

KERR (Newcastle-upon-Tyne) Congratulations on what could be a very important advance for all of us. I am pleased to hear that these are naturally occurring
substances which are believed to be non-toxic. Can you tell us how they occur naturally? Are they licensed food additives only in their natural form or in their combined form? How far have you got with getting them on the market?

SCHNEIDER The natural polymers are ‘natural’ in as much as they are not charged. Once they are charged they become medications and have to go through the Regional Drugs and Medicines Authorities.

RITZ (Heidelberg) If your claims are confirmed you may have found, as we say in German, “Sie haben das Ei des Colombus gefund”. I have one difficulty with your data, on the ordinate you plotted phosphate, and you claimed that 1g of the compound binds 0.2—0.3g phosphate, are you referring to phosphorus or phosphate?

SCHNEIDER It’s phosphate.

RITZ Therefore the efficacy is quite low?

SCHNEIDER We have compared the efficacy to other aluminium containing phosphate binders currently available and from this point of view the efficacy is quite high, for example three times as high as Aludrox®.

BOMMER (Munich) Our problem is the amount of phosphate binders the patients have to take. We can confirm that, in the few patients we have studied, the plasma phosphate falls as much as or even more than with aluminium hydroxide. We find that we need only 70 per cent of the new binder compared with aluminium hydroxide, is this your experience?

SCHNEIDER I have the same experience. There are some patients maintained with 2—3g daily with the natural polymer while others require up to 8—9g daily to maintain adequate serum phosphate concentrations. Up to 10g daily may be taken without problems.

FOURNIER (Chairman) This represents, for me, a breakthrough in the treatment of uraemic hyperparathyroidism. It would be interesting to undertake a metabolic balance study of phosphate and calcium with this new preparation. I don’t know if the fall in plasma calcium represents a negative calcium balance.

SCHNEIDER We have some studies underway on this problem, but I can’t give any results as yet.