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# The evaluation of novel mixed metal hydroxy-carbonates as phosphate binders: an in-vivo study in the rat

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**Abstract**

A number of novel phosphate binders based on mixed metal hydroxide structures incorporating Fe and Ca, or Fe and Mg (classified as CT, Crosfield test compounds), were compared with the established phosphate binders $Mg(OH)_2$, $Al(OH)_3$, $CaCO_3$ and a commercial hydrotalcite (Al- and Mg-based) using a rat model. The changes in urine and soluble faecal phosphate were used to evaluate efficacy of phosphate binding. The binders were mixed into a standard rat maintenance food at a concentration of 1% (w/w). Four rats were used for each binder study group and fed over 7 days. Urine and faeces were collected (in a metabolic cage) over the last 24-h study period and the phosphate content measured. The urinary phosphate was significantly reduced ($P < 0.001$) with CTFeCa ($72 \pm 44$ $\mu$m), CTFeMg ($13 \pm 4$ $\mu$m), CT100 ($26 \pm 11$ $\mu$m), and $Mg(OH)_2$ ($65 \pm 53$ $\mu$m), compared with control ($766 \pm 188$ $\mu$m), $Al(OH)_3$ ($1256 \pm 279$ $\mu$m), and $CaCO_3$ ($857 \pm 25$ $\mu$m). The soluble phosphate content of the faeces was significantly reduced ($P < 0.05$) by up to 60% with CTFeCa, CTFeMg and $Mg(OH)_2$, and up to 40% with CT100 and $Al(OH)_3$, compared with 30% in controls and 10% with $CaCO_3$. The new mixed metal hydroxy-carbonate compounds based on FeCa or FeMg are effective phosphate binders in-vivo and warrant further testing in patients.

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## Introduction

Hyperphosphataemia, defined as a serum phosphate concentration greater than 1.7 mmol $L^{-1}$, occurs in 64% of haemodialysis patients (Ansell & Feest 1997), and may lead to secondary hyperparathyroidism and renal osteodystrophy (Ghazali et al 1993; Knochel & Agarwal 1996). The treatment of hyperphosphataemia involves administration of compounds to complex with or bind phosphate in the gastrointestinal tract, thus preventing its absorption. Conventionally, aluminium salts have been used as phosphate binders. However, studies show that aluminium in these compounds is absorbed from the gastrointestinal tract and is not removed by dialysis (Powell & Thompson 1993). Thus, haemodialysis patients are likely to accumulate significant amounts of aluminium (Davenport & Roberts 1989). This accumulation of aluminium may cause dialysis encephalopathy, microcytic anaemia and osteomalacia (Alfrey et al 1976; Parkinson et al 1979; Short et al 1980). The current binders of choice are therefore calcium salts, which have been used with only varying degrees of success (Ghazali et al 1993; Pflanz et al 1994). Other metal-based compounds have been put forward as viable alternatives, including magnesium, lanthanum and zirconyl salts (O'Donovan et al 1986;

Oe et al 1987; Graff & Burnell 1995a, b; Dewberry et al 1997), although safety associated with long-term ingestion may be an issue. Hyperphosphataemia may also be controlled by dietary phosphate restriction (Knochel & Agarwal 1996); however, major problems are associated with this treatment including low patient compliance due to the unpalatable nature of the diet and possible hypocalcaemia.

Thus, there is a need for a compound with a high capacity for phosphate binding in ingested food, which can be administered over long periods of time with low toxicity. Studies have shown that hydrotalcite ($Al_2Mg_6(OH)_{16}.CO_34H_2O$) as CT100, a proprietary preparation from Crosfield Ltd (Warrington, UK), precipitates phosphate from solution (Ookubo et al 1992; Rankin et al 1997). CT100 and the mixed metal hydroxy-carbonates, CTFeMg and CTFeCa, have also been shown to precipitate phosphate from a food slurry (Rankin et al 1997). Here we report the results of in-vivo studies in rats treated with CT100, CTFeCa and CTFeMg as phosphate binders compared with $Al(OH)_3$, $Mg(OH)_2$ and $CaCO_3$. The study used healthy rats, not in renal failure, and for this reason the urinary phosphate output and soluble faecal phosphate were used to indicate reduction in phosphate absorption and phosphate precipitation in the intestine. This procedure was relatively uncomplicated and therefore facilitated comparison of a range of novel phosphate binders with a range of compounds used in clinical practice.

## Materials and Methods

The following chemicals were GPR grade from BDH/Merck (Poole, UK), unless otherwise stated: $CaSO_4$, $Fe_2(SO_4)_3.xH_2O$ (technical grade), $MgSO_4$, $CaCO_3$, NaOH, and 70% nitric acid (redistilled, 99.99% purity). $Al(OH)_3$ and $Mg(OH)_2$ were obtained from Sigma (Poole, UK). The altacite CT100 was obtained from Crosfield Ltd (Warrington, UK); CT indicates a Crosfield test compound. Phosphate binders were incorporated into the standard rat diet rat/mouse maintenance No1 food pellets prepared by Lilico (Betchworth, Surrey, UK) containing 0.5% total phosphorus as 0.21% phytate and 0.29% available phosphorus.

### Production of CT compounds

CTFeCa and CTFeMg were produced in the laboratory by the following standard procedure for mixed metal hydroxy-carbonate (altacite) preparations (Reichle 1986). The altacite materials are based on $metal^{3+}$ and $metal^{2+}$ structures and replacement of the ions with $Fe^{3+}$ and $Ca^{2+}$ or $Mg^{2+}$, respectively, in defined ratios (usually 1 mol $Fe^{3+}$ and 3 mol $Mg^{2+}$) form layered structures similar to altacite. $Metal^{2+}$ sulfate (6 mol) and $metal^{3+}$ sulfate (2 mol) were dissolved in 4 L de-ionized water. In a separate flask, 16 mol NaOH and 5 mol $Na_2CO_3$ were dissolved in 4 L de-ionized water. The two solutions were pumped using peristaltic pumps into a flask with an overflow at approximately 2 L, the rate of addition of the solutions being such that when mixed, the resulting suspension had a pH of 10.0–10.5. After discarding the first litre, by which time a steady state had been established, 3–4 L of overflowing slurry was collected. This was vacuum filtered using a Buchner flask and washed three times with 1 L de-ionized water. To allow incorporation into rat food, the wet cake compound was dried to constant dry weight at 50°C and ground with a mortar and pestle.

### In-vivo studies in the rat

Twenty-eight rats (Sprague-Dawley), 275–307 g, were divided into seven groups, of four rats each. The phosphate binders were incorporated into the rat food at a concentration of 1% (w/w). Each group was fed a single diet freely for 7 days and had unlimited access to de-ionized water. Rats were then weighed and transferred to metabolic cages (metabowls) for 24 h to avoid mixing the faeces and urine with the food. In these cages they received 18 g of the control diet (without the binders) and unlimited access to water. Total 24-h urine and faecal output was collected during this time. At the end of the treatment periods, rats were re-weighed and a blood sample was obtained via the carotid artery under anaesthesia with 60 mg $kg^{-1}$ sodium pentobarbitone (Sagatal).

### Preparation of faeces and urine

Due to the design of the metabowls, the rat faeces were unavoidably contaminated with small amounts of the control food from the diet and there was also slight contamination of the urine. Before analysis, food was separated from the urine by centrifugation for 5 min at 1500 rev $min^{-1}$. The food pellet was discarded. Contaminating particulate food was removed from the faeces using forceps and the stool sample weighed. Total faecal samples from each rat were mixed to ensure homogeneity and duplicate 1-g samples weighed. The percentage hydration of the stool was calculated after

freeze-drying to constant weight. Because the presence of phosphate binders in the food will potentially contaminate faecal collections and thus invalidate faecal analysis, the collections were carried out with all the rats taking the same control diet over the final 24 h of the study. The gastrointestinal transit time is between 12 and 24 h, therefore urine and faecal content represents intake during the period of phosphate binder treatment. For measurement of total faecal phosphate and metal ion content, freeze-dried faeces were ground with a mortar and pestle and 200 mg hydrolysed by heating to 70°C for 4 h with 7 mL concentrated nitric acid in polypropylene test tubes. The faecal digests were diluted to 50 mL with de-ionized water in acid washed 125 mL Nalgene containers. For measurement of soluble faecal phosphate and metal ion content, a 1.5-g sample of stool was suspended in 15 mL de-ionized water. After homogenization and centrifugation at 3000 rev $min^{-1}$ for 45 min, the supernatant was filtered through glass wool to remove contaminating particulate matter and stored at −20°C.

### Analytical methods

Phosphate, iron and calcium were determined in the faecal digest solutions, urine and plasma/serum using standard Boehringher Mannheim chemistries on a Hitachi 911 autoanalyser. Magnesium was measured in the faecal digest solutions, urine and plasma using flame atomic absorption spectrometry. Urine and plasma aluminium were measured using graphite furnace atomic absorption spectrometry (model 400; Varian Ltd, Walton-on-Thames, UK). Differences between treatment groups were assessed using both analysis of variance and Student's *t*-test with $P < 0.05$ considered significant.

## Results

### Weight changes

All rats were weighed daily during the course of the study to ensure that food modified by the addition of phosphate binding compounds did not affect weight gain. During the 7-day equilibration period, groups of rats treated with CTFeCa, CTFeMg, $Mg(OH)_2$, $CaCO_3$ or CT100 showed a similar range of mean weight gain from 38 to 53 g. However, the controls and rats treated with $Al(OH)_3$ showed a lower weight gain of $3 \pm 1.5$ g (mean ± s.e.m.). During the 24-h period with the control diet, there was no significant change in the bodyweight of the rats.

### 24-h urine and faecal excretion

Mean urine volume excretion by rats treated with $Mg(OH)_2$ or CT100 was significantly lower than that in the controls, and in rats treated with $CaCO_3$ and $Al(OH)_3$ (Table 1). Rats treated with CTFeMg excreted

**Table 1** Urine volume, faecal output and faecal hydration for rats treated with phosphate binding compounds.

| Treatment | Urine volume (mL) | Faecal weight (g) | Faecal hydration (%) |
|---|---|---|---|
| Control | 27.3 ± 2.9 | 11.5 ± 1.1 | 56.8 ± 0.7 |
| $Al(OH)_3$ | 27.4 ± 3.9 | 11.6 ± 0.3 | 49.9 ± 0.9§ |
| $CaCO_3$ | 29.0 ± 4.1 | 17.2 ± 0.9‡ | 56.8 ± 1.8 |
| CTFeCa | 19.0 ± 5.6 | 12.0 ± 0.8 | 55.8 ± 1.0 |
| $Mg(OH)_2$ | 10.0 ± 2.0* | 14.5 ± 1.6 | 55.6 ± 1.1 |
| CT100 | 12.0 ± 1.0† | 14.7 ± 1.1 | 56.6 ± 1.4 |
| CTFeMg | 17.9 ± 1.8 | 13.4 ± 1.0 | 52.1 ± 0.6¶ |

The results are mean ± s.e.m., n = 4. *$P < 0.05$ compared with all other groups except CT100; †$P < 0.05$ compared with all other groups except $Mg(OH)_2$; ‡$P < 0.05$ compared with the control, $Al(OH)_3$, CTFeCa and CTFeMg; §$P < 0.05$ compared with all other groups except CTFeMg; ¶$P < 0.05$ compared with all other groups except $Al(OH)_3$.

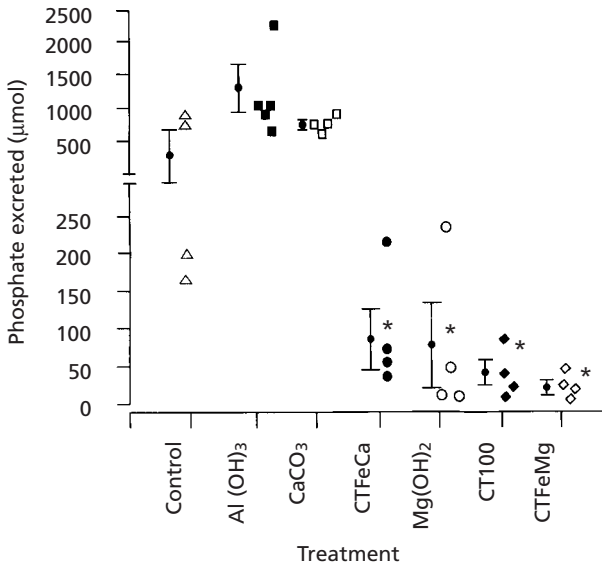


**Figure 1** Individual and mean ± s.e.m. urinary phosphate excretion for rats treated with phosphate binding compounds. Individual values of urinary phosphate excretion (μmol/24 h) were plotted for rats treated with control (△), $Al(OH)_3$ (■), $CaCO_3$ (□), CTFeCa (●), $Mg(OH)_2$ (○), CT100 (◆) and CTFeMg (◇). Mean ± s.e.m. for each group is represented by points with error bars. *$P < 0.05$ compared with $Al(OH)_3$- and $CaCO_3$-treated groups.

significantly more urine than rats treated with $Mg(OH)_2$ or CT100.

Rats treated with $CaCO_3$ excreted the greatest mean weight of faeces, significantly higher than the faecal excretion from rats treated with CTFeCa, $Al(OH)_3$ or CTFeMg (Table 1).

The effect of the phosphate binders on stool hydration was measured on duplicate samples of faeces by freeze-drying to constant weight. Groups treated with $Al(OH)_3$ and CTFeMg produced stools containing significantly lower hydration than other groups (Table 1).

### Measurement of urine and faecal phosphate excretion

Renal phosphate excretion was expressed as total $\mu$mol per 24 h. Controls and rats treated with $Al(OH)_3$ or $CaCO_3$ excreted $766 \pm 188$, $1259 \pm 279$ and $857 \pm 25$ $\mu$mol phosphate (mean $\pm$ s.e.m.), respectively (Figure 1; Table 2). These values were significantly higher than from rats treated with CTFeCa, CTMgFe, CT100 or $Mg(OH)_2$ ($72 \pm 44$, $13 \pm 4$, $26 \pm 11$ and $65 \pm 53$ $\mu$mol phosphate, respectively). The wide range of values reported for the controls may have been due to their variation in intake.

To indicate whether phosphate binders were precipitating phosphate in the rat gastrointestinal tract, total stool phosphate (bound and soluble) and soluble stool phosphate (unbound) were measured. To control for variations in faecal output and faecal hydration between groups, faceal phosphate was expressed as $\mu$mol phosphate (g dry weight faeces)$^{-1}$. Total (soluble and insoluble) phosphate (g dry weight faeces)$^{-1}$ did not differ significantly between any of the treatment groups. Faeces from rats treated with CTFeCa contained significantly less soluble phosphate than that from rats treated with $CaCO_3$ (Table 2). Mean soluble phosphate (g dry weight faeces)$^{-1}$ as a percentage of mean total phosphate (g dry weight faeces)$^{-1}$ was 41.9, 44.8, 55.9, 60.7 and 45.0% for rats treated with CTFeCa, $Mg(OH)_2$, $Al(OH)_3$, CT100 and CTFeMg, respectively. Soluble phosphate comprised 85.5% of the total in the group treated with $CaCO_3$, and up to 75% in the controls (Table 2). These results demonstrate the effectiveness of the CT compounds as binders, decreasing the soluble phosphate compared with the controls and rats treated with $CaCO_3$.

### Urine aluminium excretion, plasma aluminium concentration

The urinary excretion of aluminium, expressed as $\mu$g excreted per 24 h, for rats treated with $Al(OH)_3$ was significantly increased ($P < 0.05$) and was at least two-fold higher than rats treated with any other phosphate binder, the individual values of which were all approximately the same (Table 3). For rats dosed with $Mg(OH)_2$, $Al(OH)_3$ or $CaCO_3$, the plasma aluminium concentrations were lower than controls (Table 3). Rats treated with CTFeCa, CTFeMg or CT100 showed slightly higher plasma aluminium concentrations than the controls and significantly higher concentrations than in rats treated with conventional phosphate binders.

**Table 2** Urine and faecal phosphate excretion for rats treated with phosphate binding compounds.

| | Control | $Al(OH)_3$ | $CaCO_3$ | CTFeCa | $Mg(OH)_2$ | CT100 | CTFeMg |
|---|---|---|---|---|---|---|---|
| Urine phosphate ($\mu$mol) (n = 4) | $766 \pm 188$ (n = 3) | $1259 \pm 279$ | $857 \pm 25$ | $72 \pm 44$* | $65 \pm 53$* | $26 \pm 11$* | $13 \pm 4$* |
| Total faecal phosphate $\mu$mol (g dry weight faeces)$^{-1}$ (n = 4) | $170 \pm 32$ | $188 \pm 26$ | $213 \pm 16$ | $181 \pm 12$ | $183 \pm 17$ | $181 \pm 40$ | $206 \pm 34$ |
| Soluble faecal phosphate $\mu$mol (g dry weight faeces)$^{-1}$ (n = 4) | $130 \pm 6$ | $96 \pm 9$ | $181 \pm 9$‡ | $73 \pm 12$§ | $87 \pm 14$ | $100 \pm 15$ | $108 \pm 8$ |
| Soluble faecal phosphate % total (soluble and insoluble) | $76 \pm 10.5$ | $51 \pm 8$† | $85 \pm 4$ | $40 \pm 5$† | $48 \pm 5.2$† | $55 \pm 10$ | $52 \pm 10.5$† |

The results are mean $\pm$ s.e.m. *$P < 0.05$ compared with the control, $Al(OH)_3$ and $CaCO_3$. †$P < 0.05$ compared with the control and $CaCO_3$. ‡$P < 0.05$ compared with all other groups; §$P < 0.05$ compared with the control, $CaCO_3$ and CTFeMg.

**Table 3** The 24-h urine aluminium excretion and plasma aluminium concentration for rats treated with phosphate binding compounds.

| Treatment | Urine aluminium/24 h | Plasma aluminium (μmol $L^{-1}$) |
|---|---|---|
| Control | 0.24 ± 0.03 | 0.55 ± 0.10 |
| $Al(OH)_3$ | 1.07 ± 0.38† | 0.38 ± 0.03 |
| $CaCO_3$ | 0.50 ± 0.21 | 0.33 ± 0.05 |
| CTFeCa | 0.18 ± 0.12 | 0.66 ± 0.07* |
| $Mg(OH)_2$ | 0.17 ± 0.07 | 0.35 ± 0.08 |
| CT100 | 0.26 ± 0.09 | 0.65 ± 0.24* |
| CTFeMg | 0.31 ± 0.09 | 0.65 ± 0.05* |

The results are mean ± s.e.m. *$P < 0.05$ compared with $Al(OH)_3$, $CaCO_3$ and $Mg(OH)_2$. †$P < 0.05$ compared with all other groups. Note: blood was taken in the non-fasting state which might explain the diversity of plasma aluminium values.

### Measurement of urine calcium and magnesium excretion

The rats treated with the CT compounds showed no untoward effects on calcium excretion. Rats treated with $CaCO_3$ excreted significantly more calcium than the controls and rats treated with $Mg(OH)_2$, CT100, CTFeCa and CTFeMg, but less than rats treated with $Al(OH)_3$ (Table 4). Urinary magnesium excretion after $Mg(OH)_2$ administration was significantly higher than in rats treated with any other binder. Magnesium excretion after treatment with CTFeMg, although less than in rats treated with $Mg(OH)_2$, was higher than the controls.

### Measurement of urinary and plasma iron concentration

In all urine samples from all treatment groups, the iron concentration was at the limit of detection of the method used ($> 1$ μmol $L^{-1}$). Release of iron from the phosphate binders was assessed by plasma iron concentrations which showed no significant difference between any of the treatment groups (Table 4).

## Discussion

Treatment of hyperphosphataemia involves reducing the dietary phosphate burden and hence absorption. However, diets with a low phosphate content are unpalatable and patient compliance becomes a problem (Knochel & Agarwal 1996). Additionally, these foods are also low in calcium, which is contraindicated for patients who are often hypocalcaemic. Dietary phosphate burden is therefore controlled by ingestion of binders, reducing availability for absorption. The current therapies of choice, $CaCO_3$ and $Al(OH)_3$, are however associated with hypercalcaemia and aluminium accumulation/toxicity, respectively (Coburn & Salusky 1989; Davenport & Roberts 1989; Sherrard 1991). In addition, $CaCO_3$ is an inefficient binder and has to be used in large doses of up to 20 g per day (Schaefer et al 1988).

A previous study has demonstrated mixed metal hydroxy-carbonate compounds (CT compounds) to be superior phosphate binders in-vitro to either $Al(OH)_3$ or $CaCO_3$ (Rankin et al 1997). This study confirms the effectiveness of these CT compounds, significantly reducing rat urinary phosphate excretion compared with control rats and those treated with either $Al(OH)_3$ or $CaCO_3$. The CT compounds effectiveness in-vivo was further confirmed by a reduction in the soluble faecal phosphate compared with rats treated with $CaCO_3$. Interestingly, in rats treated with $Al(OH)_3$, a reduction in soluble faecal phosphate was not paralleled by a reduction in urinary phosphate excretion. The explanation for this is not clear but it might be related to an increased food intake during the final 24 h of the study. However the urine phosphate was relatively normal which would then indicate either good phosphate absorption or increased urinary losses. In this model, $Al(OH)_3$ is shown to be a relatively ineffective phosphate binder, as also indicated by our in-vitro studies (Rankin et al 1997).

The compounds CT100, CTFeMg and CTFeCa almost completely abolished urinary phosphate excretion when administered at the relatively low concentration of 1% (w/w) in food. It is possible that this dose was in excess of optimal requirements, suggesting similar results could be achieved with lower dosage regimes. These compounds could therefore provide efficient phosphate binding therapy at doses acceptable for daily intake.

Ookubo et al (1992) have studied the compound hydrotalcite in-vitro and shown it to be an effective phosphate binder. However, to our knowledge, this is the first study to demonstrate the effectiveness of these mixed metal hydroxy-carbonate compounds as phosphate binders in-vivo. An iron-based phosphate binder, $Fe^{3+}$ oxide–hydroxide modified dextran complex, was shown to reduce urinary phosphate concentration in the rat (Spengler et al 1996). These results may however be explained by a reduction in urine volume as opposed to binding of phosphate as the actual output of phosphate was not recorded. Additionally, the binder was administered at a high concentration of 8% (w/w) in food,

**Table 4** The 24-h urine calcium and magnesium excretion, and plasma iron concentration for rats treated with phosphate binding compounds.

| Treatment | Urine calcium (μmol) (n = 4) | Urine magnesium (μmol) (n = 4) | Plasma iron (μmol $L^{-1}$) |
|---|---|---|---|
| Control | 317 ± 94 | 6.3 ± 1.8 | 37.8 ± 11.2 (n = 3) |
| $Al(OH)_3$ | 539 ± 24.2 | 9.7 ± 0.6 | 38.5 ± 15.9 (n = 3) |
| $CaCO_3$ | 472 ± 17* | 8.7 ± 1.8 | 41.9 ± 10.8 (n = 4) |
| CTFeCa | 333 ± 80 | 5.9 ± 1.2 | 23.9 ± 5.1 (n = 4) |
| $Mg(OH)_2$ | 360 ± 62 | 17.3 ± 2.3† | 29.4 ± 7.9 (n = 3) |
| CT100 | 314 ± 20 | 9.2 ± 0.6 | 39.5 ± 10.8 (n = 4) |
| CTFeMg | 300 ± 34 | 11.4 ± 0.7 | 48.5 ± 12.5 (n = 3) |

The results are mean ± s.e.m. *$P < 0.05$ compared with all other groups except $Al(OH)_3$.
†$P < 0.05$ compared with all groups.

which may be difficult to tolerate if given to patients on a daily basis.

As phosphate binders are administered in relatively large doses over long periods of time, metal ion release, absorption and toxicity are of prime concern. Plasma aluminium concentration in rats treated with $Al(OH)_3$ or CT100 was not significantly higher than in rats treated with any other binder. This is in agreement with a study in man which reported no increase in serum aluminium, measured up to 7 h after administration of 6 g hydrotalcite (CT100) (Van der Voet & de Wolff 1986). However, as only less than 0.1 % of ingested aluminium dose is absorbed (Powell & Thompson 1993), the possible changes in the plasma will be at the limits of accurate measurement. The apparent increase with the CTFeMg and CTFeCa compounds was possibly a result of variations around such an analytical detection limit. We therefore measured urinary aluminium excretion as an indicator of intestinal uptake. Rats treated with $Al(OH)_3$ excreted at least twofold more aluminium than rats treated with any other binder and three- to fourfold more than rats treated with the CT compound, indicating relatively little aluminium absorption with this treatment. Conclusions as to the relative benefits of the hydrotalcite (CT100) in terms of aluminium release were however not completely confirmed as shown by a preliminary study showing a relatively high urinary excretion of aluminium: range 2.0–3.5 $\mu$mol/24 h after 6 g total intake of CT100 compared with a control period 1.0–2.2 $\mu$mol/24 h in healthy volunteers (n = 4) (unpublished data).

Release and absorption of iron from the CTFeCa and CTFeMg binders was of concern as iron content is regulated by absorption from the gastrointestinal tract (McCance & Widdowson 1937). There is no physiological route by which it can be excreted and daily losses are low: urine $< 0.1$ mg, skin 0.2–0.3 mg, and faeces 0.6 mg (Bothwell 1995). Rats treated with CTFeCa or CTFeMg did not show an increase in plasma iron compared with rats treated with non-iron-containing binders, and as expected, urine iron excretion was not changed, being at the limit of detection in all groups. Compared with rats treated with any other binder, there was at least a 66 % and 113 % increase in soluble faecal iron in rats treated with CTFeCa or CTFeMg, respectively. Whether this was absorbable was beyond the scope of this study, as complex factors including diet and iron store size influence non-haem iron uptake (Bothwell 1995; Cook 1990). However, as a number of haemodialysis patients are anaemic, an increased iron load may be beneficial (Remuzzi & Rossi 1996).

Different magnesium salts have been shown to have efficacy as phosphate binders. Magnesium carbonate has been shown to be an efficient binder (O'Donovan et al 1986) whereas magnesium hydroxide was relatively ineffective or poorly tolerated due to its laxative properties (Guillot et al 1982; Oe et al 1987). In this study none of the groups treated with $Mg(OH)_2$, CT100 or CTFeMg showed an increase in faecal hydration compared with controls, $CaCO_3$ and or $Al(OH)_3$, suggesting a dose that was well tolerated. Also, the urine and serum magnesium were not elevated in rats treated with CTFeMg or CT100, suggesting that Mg absorption from these compounds was low in this animal model.

In summary, the mixed metal hydroxides, CTAlMg (CT100), CTFeMg and CTFeCa are all high-capacity phosphate binders when administered in-vivo to rats at low doses. This study indicates that they are likely to have limited toxicity, although long-term studies are required to evaluate iron, aluminium and magnesium

absorption. These compounds may present effective alternatives to the currently prescribed phosphate binders.

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