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Renagel® efficacy in severe secondary hyperparathyroidism

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RESUMEN

Histórico: *Los pacientes en hemodiálisis desarrollan con frecuencia hipercalcemia e hiperfosfatemia poniendo problemas de tratamiento con los tradicionales quelantes que contienen calcio o aluminio. RenaGel® (sevelamer hydrochloride) es un quelante del fósforo que no produce alteraciones de los niveles de calcio y de aluminio. Todavía es un fármaco caro, por lo que se exige una selección de enfermos con hiperparatiroidismo secundario moderado a grave. Nos parece importante que en ninguno de los estudios ya efectuados con el RenaGel® se incluían pacientes con hiperparatiroidismo grave.*

Métodos: *Nuestro estudio pretendió determinar la eficacia quelante de fósforo del RenaGel®, en pacientes en hemodiálisis con hiperparatiroidismo grave. Como objetivos secundarios determinamos las variaciones de la hormona paratiroidea, del calcio sérico, lípidos [colesterol de baja y alta densidad, triglicéridos y Lipoproteína(a)], albúmina, ácido úrico y bicarbonato. Todos los quelantes del fósforo se suspendieron una semana antes de la introducción del RenaGel®. Se incluyeron en nuestro estudio 18 pacientes de edad adulta en hemodiálisis, con PTHi de 810 ± 330 pg/ml después del «pre-treatment washout». El nuevo quelante de fósforo ha sido administrado durante 12 semanas, iniciándose a una dosis media de 2,4 ± 0,4 g por día y se siguió ajustando la dosis intentando alcanzar un nivel de fósforo por debajo de 6,5 mg/dl.*

Resultados: *Después del RenaGel® la variación del fósforo fue de -0,7 ± 1,5 mg/dl (P < 0,05), de 0,5 ± 1,0 mg/dl (P < 0,05) del calcio y de -4,0 ± 12,4 mg^2/dl^2 (P = NS) del producto fosfocálcico. La respuesta quelante al sevelamer se definió a las 4 semanas de tratamiento. En los «respondedores» (n = 11) el fósforo descendió de 7,2 ± 1,2 mg/dl para 6,7 ± 1,0 mg/dl después de 4 semanas con RenaGel® (P = 0,04). La PTHi se estabilizó (820 ± 360 pg/ml* vs *810 ± 330 pg/ml) pero la fosfatasa alcalina aumentó (14,3 ± 14,4 U/l; P < 0,01). El LDL colesterol se redujo en -35 ± 10 mg/dl (P < 0,01), el HDL colesterol tuvo una tendencia creciente (3,0 ± 8,1 U/l; P = NS), los triglicéridos disminuyeron 38 ± 56 mg/dl (P < 0,05) y la Lipoproteína(a) no cambió significativamente. La albúmina aumentó 0,1 ± 0,2 g/l (P < 0,05), el ácido úrico disminuyó 0,8 ± 1,2 mg/dl (P < 0,05) y el bicarbonate se mantuvo estable.*

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Conclusiones. *RenaGel® fue un quelante del fósforo eficaz en la major parte de nuestros pacientes en hemodiálisis con hiperparatiroidismo grave. La «respuesta» quelante del fósforo de Sevelamer pudo ser prevista al final de las primeras 4 semanas de tratamiento pero no hemos identificado ningún factor predictivo de esa «respuesta». El perfil lipídico mejoró con la excepción de la estabilidad de la Lipoproteína(a). Una selección inicial de los pacientes con hiperparatiroidismo grave para la administración del RenaGel® nos parece correcta por el alto precio de este quelante en nuestro país.*

Palabras clave: ***Hemodiálisis. Hiperfosfatemia. Hiperparatiroidismo secundario grave. RenaGel®. Sevelamer.***

RENAGEL® EFFICACY IN SEVERE SECONDARY HYPERPARATHYROIDISM

SUMMARY

Background. *Haemodialysis patients frequently have simultaneous hypercalcemia and hyperphosphatemia, posing a therapeutic dilemma for the traditional calcium —and aluminum— based binders. RenaGel® (sevelamer hydrochloride) is an effective phosphate binder without changes in serum calcium or aluminum levels. However being an expensive medication it is currently used mainly for patients with moderate to severe secondary hyperparathyroidism. However most of the previous studies have not included patients with severe secondary hyperparathyroidism.*

Methods. *Our purpose is to determine RenaGel® binder efficacy in haemodialysis patients with severe secondary hyperparathyroidism. As a secondary purpose we have followed the variations of parathyroid hormone, serum calcium, serum lipids [low- and high-density lipoprotein cholesterol, triglycerides and Lipoprotein(a)], uric acid and bicarbonate. All phosphate binders previously used were suspended one week before RenaGel® prescription. Our study included 18 adult haemodialysis patients, with PTHi of 810 ± 330 pg/ml after the «pre-treatment» washout. The binder was administered during 12 weeks, beginning with a mean dose of 2.4 ± 0.4 g daily and adjusted to obtain serum phosphorus under 6.5 mg/dl (at the end of the study, the mean RenaGel® dose was 2.8 ± 0.6 g daily.*

Results. *The mean changes after RenaGel® in serum phosphorus was –0.7 ± 1.5 mg/dl (P < 0.05), in serum calcium was 0.5 ± 1.0 mg/dl (P < 0.05) and in calcium x phosphate product of -4.0 ± 12.4 mg/dl (P = NS). «Post-treatment» the PTHi levels remained stable (820 ± 360 pg/ml vs 810 ± 330) but serum alkaline phosphatase increased (14.3 ± 14.4 U/l; P < 0.01). LDL cholesterol serum levels decreased by -35 ± 10 mg/dl (P < 0.01), HDL cholesterol showed a trend to increase (3.0 ± 8.1 U/l; P = NS), triglycerides decreased by 38 ± 56 mg/dl (P < 0.05) and Lipoprotein(a) remained stable. Serum albumin increased by 0.1 ± 0.2 g/L (P < 0.05), uric acid decreased -0.8 ± 1.2 mg/dl (P < 0.05) and bicarbonate remained unchanged.*

Conclusions. *RenaGel® is an effective phosphate binder, even in haemodialysis patients with severe secondary hyperparathyroidism. The lipid profile improved with the treatment, with the exception of Lipoprotein(a) stabilization. Selection of patients with severe secondary hyperparathyroidism at the beginning of RenaGel® disposal, for economic reasons is debatable, but could be correct.*

Key words: ***Haemodialysis. Hyperphosphatemia. RenaGel®. Seconday hyperparathyroidism. Sevelamer***

INTRODUCTION

The management of secondary hyperparathyroidism and hyperphosphatemia with vitamin D metabolites, dietary phosphorus restriction and phosphorus binders is often not enough for dialysis patients. Hypercalcemia, hyperphosphatemia and elevated calcium × phosphorus product are relatively common and severe secondary hyperparathyroidism may require parathyroidectomy[1].

Phosphate binders are frequently withdrawn, because of hypercalcemia or elevated calcium × phosphorus product in the case of calcium based binders, or fearing toxicity of aluminum based binders (osteomalacia, myopathy, dementia and microcytic, hypocromic anaemia)[2,3]. From four to 12 g of calcium carbonate daily is generally required to prevent hyperphosphatemia[4]. Calcium acetate is an alternative, especially at neutral pH[5].

The aluminum accumulation in the bones and other tissues is due to renal failure, since the kidney is the principal excretion way of this element. Besides that, magnesium carbonate and magnesium sulphate have been abandoned as phosphate binders because of magnesium accumulation and low efficacy.

Normalization of serum phosphorus is crucial to manage secondary hyperparathyroidism[6]. Therefore, the use of non-calcium and non-aluminum phosphate binders is welcomed on this therapeutic field.

RenaGel®, a cross-linked poly(allylamine hydrochloride), binds 2.6 mmol of phosphate at an estimated concentration of 5 mM[7] and is resistant to digestive degradation and it is not absorbable by the gastrointestinal tract[1]. Short-[8-9] and long-term[1] studies showed that RenaGel® is as effective as calcium carbonate or acetate in the hyperphosphatemia control, promotes a good control of hyperparathyroidism with normal serum calcium concentrations and significant reductions of calcium × phosphorus product.

Although RenaGel® proved efficacy as phosphate binder usually it is not administered in haemodialysis patients with severe secondary hyperparathyroidism. PTHi level of Chertow study was 287 pg/ml (mean)[1], at Goldberg patients it was of 292 pg/ml (median)[10], and of 316 pg/ml (median) at Slatopolsky study for the RenaGel® Study Group[11].

Furthermore, RenaGel® induces positive changes in the lipid profile, with 20-30% decreases in LDL-cholesterol and 5-15% increases in HDL-cholesterol. These changes related to RenaGel® binding of bile acids leading to an increase of faecal bile acid excretion and to a LDL-cholesterol lowering[6].

The aim of our study was to determine RenaGel® phosphate binder efficacy on haemodialysis patients with severe secondary hyperparathyroidism.

METHODS

Subjects

Eighteen patients participated in this study, out of 210 patients that were dialyzed on our two haemodialysis clinics (NorDial and CentroDial). Inclusion criteria were PTHi always above 250 pg/ml on the previous 6 months, age over 18 years, on thrice-weekly haemodialysis for at least 12 months and regular administration of calcium and/or aluminum phosphate binders, with or without vitamin D metabolite replacement therapy. As exclusion criteria, we have selected previous partial parathyroidectomy, major intestinal surgery, gastrointestinal disease, drug addiction, HIV infection, malignancy and uncontrolled diabetes mellitus. The mean age of these 18 patients at the beginning of the study was 47.6 ± 15.3 years old (range 25-70). Eleven patients were of masculine gender (61%) and all were Caucasians. Table 1 displays their baseline characteristics.

Protocol

It was obligatory a written informed consent to all patients enrolled. The study started with an ini-

Table I. Baseline clinical characteristics of the patients (n = 18)

Age (years)	47.6 ± 15.3
Gender (% female)	39
Primary renal disease	
Unknown	5
Glumerulonephritis	4
Hypertension	2
Chronic tubulointersticial nephritis	2
Other	5
Time on dialysis (years)	8,8 ± 5,4 [1.1-17.9]
Previous kidney transplantation	2
Kt/Vsp* (high-flux haemodialysis)	1.97 ± 0,27
PNAn (g/kg/day)	1.33 ± 0.29
Dialysis session time (min)	217 ± 22
Vitamin D metabolite	
Intravenous	12
Oral	1
None	5
Dialysate calcium (mEq/l)	
2.5	9
2.75	9

*Kt/Vsp (index of haemodialysis dose, single-pool).

tial laboratory *screening,* followed by 1 week of calcium and aluminum phosphate binders «pre-treatment» washout. RenaGel® was administrated during 12 weeks (fig. 1), beginning with a mean dose of 0.8 ± 1.0 mg t.i.d. (median 0.8 g t.i.d.) and the doses were changed in order to obtain serum phosphorus lower than 6.5 mg/dl. Serum phosphorus and calcium were monitored bi-monthly. PTHi, serum lipids [low- and high-density lipoprotein cholesterol, triglycerides and Lipoprotein(a)], uric acid and bicarbonate were determined monthly. The fasting laboratory tests were always obtained in the morning before the mid-week dialysis session, even if it was necessary to anticipate their dialysis schedule. We did not change our protocols or dietary restrictions throughout the study. Supplemental carbonate calcium was allowed if serum calcium fell under 9.0 mg/dl. Dialysate calcium remained in the same value (2.6 ± 0.1 mEq/l). For the study completion, all binders were discontinued after RenaGel® treatment.

Statistical analysis

Continuous variables were presented as mean ± SD or as medians when the values were skewed. Their comparison was performed with Student's t-test or Wilcoxon rank test, as appropriated. Categorical variables were compared with the Fisher's exact test. RenaGel® phosphate binder effect was analysed using the changes of serum phosphorus throughout 12 weeks.

RESULTS

All the patients enrolled in the study (n = 18) have succeeded on finishing it. They were taking calcium carbonate (n = 9; 7.8 ± 4.0 g/day), aluminum hydroxide with or without calcium carbonate (n = 4; 0.8 ± 0.9 g/day), or none, immediately before the «pre-treatment» phosphate binder washout. Nevertheless, all of these patients have been exposed to both binders throughout their dialysis life (8.8 ± 5.4 years). None of them has been previously treated with RenaGel®.

The mean daily dose of RenaGel® prescribed was 2.7 ± 0.6 g. RenaGel® mean dose by the end of the study was 2.3 ± 0.5 g daily. The therapy compliance determined by tablet count was 100%.

Phosphorus

The mean serum phosphorus at the baseline was 6.6 ± 0.9 mg/dl. After the «pre-treatment» binder washout it raised to 6.9 ± 1.0 (P = NS). After sevelamer treatment the mean serum phosphorus lowered to 6.3 ± 1.3 mg/dl (P = 0.041) corresponding to a mean change of -0.7 ± 1.5 mg/dl comparing with the «pre-treatment» values (fig. 2).

Eleven patients (61%) showed a positive binder response reducing their phosphorus from 7.2 ± 1.2 mg/dl to 5.6 ± 1.0 mg/dl (p = 0.0002; fig. 3). For the seven «non-responders» the phosphorus raised from 6.5 ± 0.6 mg/dl to 7.4 ± 0.9 mg/dl (p = 0.004; fig. 3). There were no baseline differences on these two groups concerning age (48 ± 15

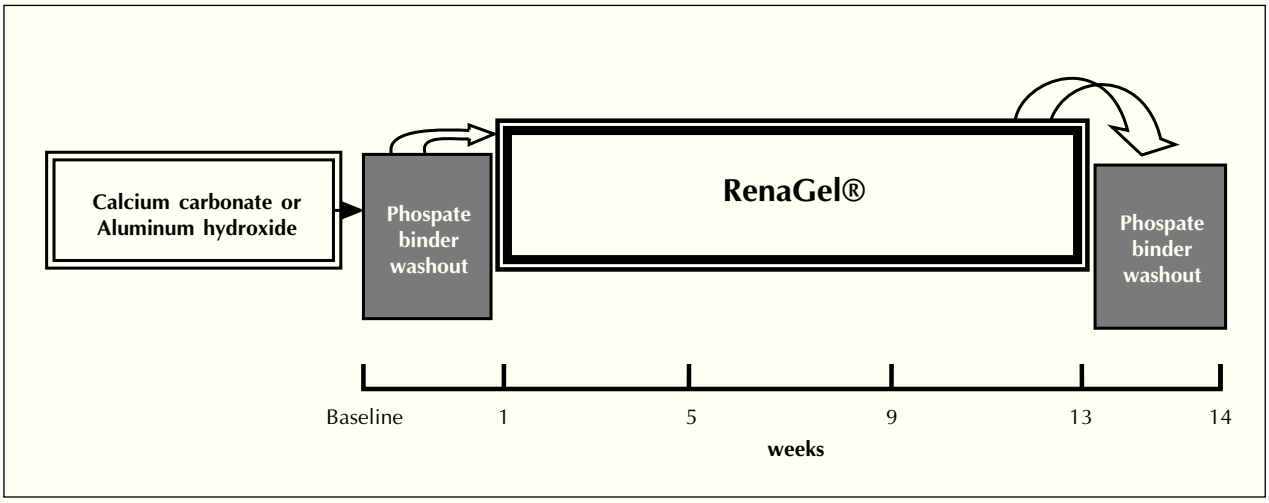

Fig. 1.—Study protocol.

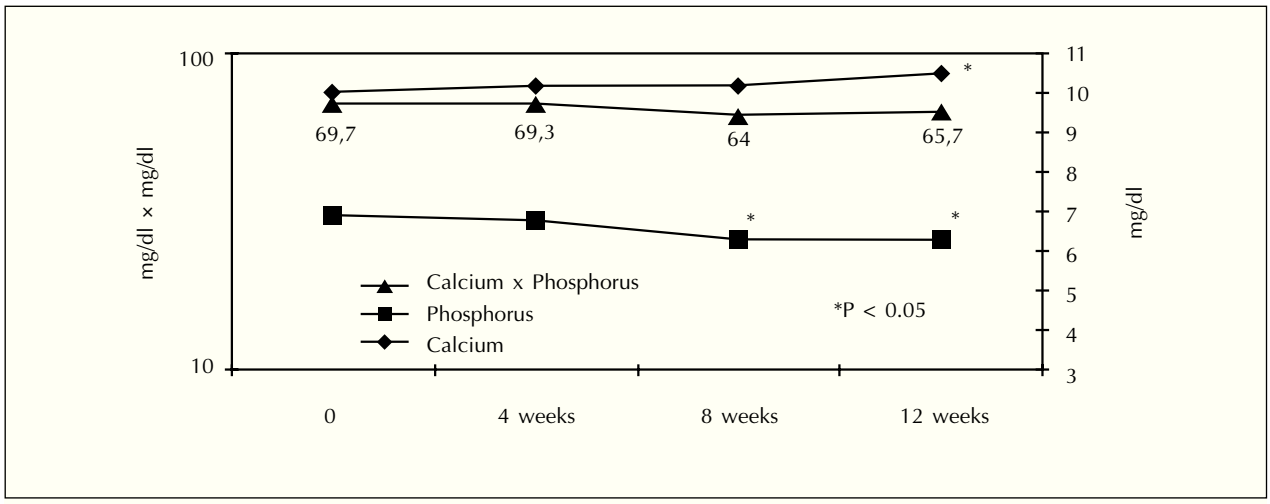

Figure 2.—Phosphorus, calcium and calcium x phosphorus product variations.

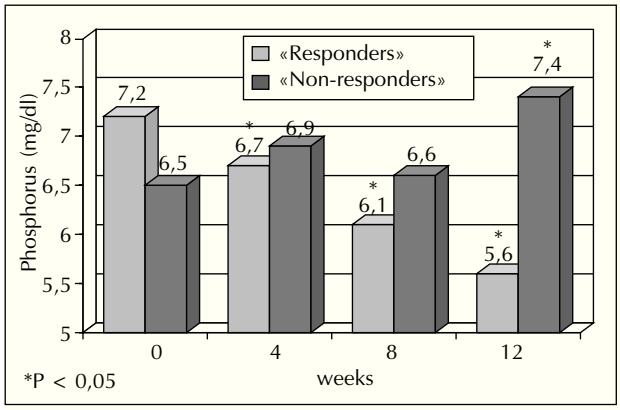

Fig. 3.—Phosphorus changes in sevelamer responders (n = 11) and non = responders (n = 7).

years-old *vs* 46.2 ± 16.8 years-old; P = NS), gender (7 males / 4 females *vs* 4 males / 3 females; χ^2 = NS), dialysis time (8.3 ± 6.0 years *vs* 9.6 ± 4.4 years; P = NS), aetiology of primary renal disease and PTHi (806 ± 349 pg/ml *vs* 813 ± 315 pg/ml; P = NS).

The sevelamer binder response in our study could be estimated after the first 4 weeks of treatment. In the «responders» group (n = 11) the phosphorus declined from 7.2 ± 1.2 mg/dl to 6.7 ± 1.0 mg/dl (P = 0.04). At the 8th week there was a greater pronounced phosphorus decline (7.2 ± 1.2 mg/dl to 6.1 ± 1.4 mg/dl; P = 0.008). «Non-responders» showed stability of serum phosphorus at the 4th week (6.5 ± 0.6 mg/dl *vs* 6.9 ± 0.6 mg/dl; P = NS) and 8th week (6.5 ± 0.6 mg/dl *vs* 6.6 ± 1.2 mg/dl; P = NS) as seen in figure 3.

There was a trend for a higher number of patients treated with vitamin D metabolites after 12 weeks with sevelamer (15 *vs* 13; P = NS). The mean dose of intravenous vitamin D was slightly higher after the 12 weeks of sevelamer therapy (1.6 ± 0.5 µg thrice weekly at the study end for 12 patients *vs* 1.4 ± 0.5 µg thrice weekly for 12 patients after the initial binder washout; P = NS). Three patients have changed from intravenous vitamin D (Calcigex®) to oral vitamin D (Rocaltrol®). Two patients, who were not under vitamin D due to high calcium × phosphate product, were medicated with Calcigex® after 4 weeks of sevelamer. One patient changed from oral vitamin D (Rocaltrol®) to intravenous vitamin D (Calcigex®), and the last three patients remained without vitamin D replacement due to continuous high calcium × phosphate product.

It is noteworthy that these three patients did not differ from the patients that were medicated with Vitamin D (either orally or intravenously) concerning serum phosphorus at baseline (6.9 ± 0.6 mg/dl *vs* 6.5 ± 0.9 mg/dl; P = NS). Also, after binder washout (6.9 ± 0.7 mg/dl *vs* 7.0 ± 1.1 mg/dl; P = NS) and after 12 weeks of sevelamer (6.7 ± 0.7 mg/dl *vs* 6.2 ± 1.4 mg/dl; P = NS) they maintained similar phosphorus levels. However, there was a trend to higher sevelamer binder response in patients on vitamin D supplements (median phosphorus variation: -0.8 mg/dl *vs* + 0.1 mg/dl; P = NS).

Calcium

The mean serum calcium at the baseline was 10.4 ± 0.8 mg/dl. Following the «pre-treatment» binder washout calcium has decreased to 10.0 ± 0.5 (P = 0.06). After sevelamer treatment the mean serum calcium raised to 10.5 ± 0.8 mg/dl (P = 0.02) corresponding to a mean change of + 0.5 ± 1.0 mg/dl comparing to the «pre-treatment» values (fig. 2). After one week of sevelamer, withdrawing («post-treatment» washout without any phosphorus binder) there was no significant change in serum calcium. The global incidence of hypercalcemia (serum calcium ≥ 11.0 mg/dl) was 12.6% throughout the treatment, but at baseline and at the end of the study, four patients (22.2%) showed hypercalcemia.

The 11 patients that responded to sevelamer with phosphorus lowering registered a raise in calcium (10.0 ± 0.5 mg/dl *vs* 10.8 ± 0.8 mg/dl; P = 0.01) and the remaining seven patients maintained calcium stability (10.1 ± 0.6 mg/dl *vs* 10.1 ± 0.7 mg/dl; P = NS).

It was necessary to reintroduce calcium carbonate in six patients (6.0 ± 2.7 g daily) but in only one patient, this was due to hypocalcemia. In the other five, it was reintroduced due to phosphorus levels persistently higher than 6.5 mg/dl with the maximum dose of sevelamer that we could afford (3.6 g daily). Aluminum hydroxide was never reintroduced throughout the study.

Calcium × phosphate product

The mean calcium × phosphorus product at the baseline was 67.6 ± 8.4 mg/dl. After the «pre-treatment» binder washout it raised to 69.7 ± 10.7 (P = NS). Twelve weeks of sevelamer treatment caused a decline of the mean serum calcium x phosphorus product to 65.7 ± 10.8 mg/dl (P = NS) corresponding to a mean change of -4.0 ± 12.4 mg/dl comparing with the «pre-treatment» values (fig. 2). From the end of the sevelamer treatment to the end of the «post-treatment» binder washout there was a non-significant trend towards an elevated product (65.7 ± 10.8 mg/dl *vs* 70.1 ± 15.5 mg/dl; P = NS). The global incidence of calcium × phosphorus product above 60 mg/dl was notorious (75.7%). Nevertheless, we must note that at the baseline 77.8% of the patients registered the same elevated product. Figure 2 displays the phosphorus, calcium and calcium × phosphorus product during the study.

Parathyroid hormone

After the «pre-treatment» binder washout, the mean PTHi was 810 ± 330 pg/ml (median: 714 pg/ml). At the end of the study PTHi remained stable (820 ± 360 pg/ml; P=NS). The PTHi stability was however associated to elevated calcium × phosphorus product (75.7%) and significant hypercalcemia (12.6%).

It is remarkable that the 11 patients responders to sevelamer with phosphorus lowering also registered a lowering tendency of PTHi (806 ± 349 pg/ml *vs* 704 ± 144; P = NS). On the contrary sevelamer «non-responders» have showed a tendency to raise their PTHi (813 ± 315 *vs* 1,034 ± 551 pg/ml; P = NS).

Serum lipids

The LDL cholesterol declined with the RenaGel® treatment from 154 ± 32 mg/dl to 132 ± 25 mg/dl (-23%; P < 0.01). The HDL cholesterol showed a trend to increase from 41.6 ± 7.1 mg/dl to 43.9 ± 10.2 mg/dl (7%; P = NS). Triglycerides decreased from 219 ± 82 mg/dl to 181 ± 62 mg/dl (p < 0.05) and Lipoprotein(a) remained stable (131 ± 149 mg/dl *vs.* 134 ± 127 mg/dl; P = NS).

Other laboratory parameters

Serum albumin increased from 3.9 ± 0.2 g/L to 4.0 ± 0.3 g/L (+3.7%; P < 0.05). Alkaline phosphatase increased by 14.3% (100 ± 30 *vs* 115 ± 36 U/L; P < 0.01). Uric acid lowered by 9% (8.8 ± 1.5 *vs* 8.0 ± 0.7 mg/dl; P < 0.05) and bicarbonate remained unchanged (20.0 ± 2.0 vs 20.3 ± 0.3 mmol/l; P = NS).

DISCUSSION

The treatment with aluminum phosphate binders in renal failure patients leads to absorption of aluminium, which contributes to osteoporosis, encephalopathy and proximal myopathy[3,12]. Calcium carbonate and acetate are good phosphate binders, but are linked to a high prevalence of hypercalcemia[2,4-5]. The advent of non-calcium and non-aluminum phosphate binders as RenaGel® is therefore absolutely necessary and wanted by the nephrologists all over the world.

RenaGel® proved efficacy as phosphate binder in short-[8-9] and long-term[1] studies. Nevertheless, it was never used in haemodialysis patients with severe se-

condary hyperparathyroidism. For instance, the PTHi level of Chertow study patients was 287 pg/ml (mean)[1], on Goldberg patients it was of 292 pg/m (median)[10] and of 316 pg/ml (median) on Slatopolsky study for the RenaGel® Study Group[11].

At our 2 haemodialysis centres we faced the possibility to use this new phosphate binder, at our own expense, on a limited period (12 weeks). On a daily basis, almost all nephrologists examine and treat patients with severe secondary hyperparathyroidism associated with elevated calcium × phosphorus product, hypercalcemia or hyperphosphatemia. Our primary goal in this study was to determine RenaGel® phosphate binder efficacy in haemodialysis patients with severe secondary hyperparathyroidism (mean PTHi 820 ± 360 pg/ml). The secondary objectives were to determine the effects of RenaGel® on parathyroid hormone, serum calcium, serum lipids [low- and high-density lipoprotein cholesterol, triglycerides and Lipoprotein(a)], uric acid and bicarbonate.

Serum phosphorus has an important role in the development of parathyroid hyperplasia[13] and at our study RenaGel® treatment reduced the serum phosphorus (–0.7 ± 1.5 mg/dl; P < 0.05). Nevertheless, the elevated calcium × phosphorus product at the study end (65.7 ± 10.8 mg/dl; P = NS), mainly explained by the elevated serum calcium (10.5 ± 0.8 mg/dl; P = 0.02) is problematic. Furthermore, the stability of PTHi during the study may be explained by the maintenance of this high level of calcemia precluding us from higher doses of vitamin D supplementation, although we must emphasize that the follow-up was short.

The relative low reduction of serum phosphorus that we have achieved (6.9 ± 1.0 to 6.3 ± 1.3 mg/dl; P = 0.041) is inferior to the reduction of Slatopolsky study (9.1 ± 2.4 mg/dl to 6.6 ± 1.9 mg/dl; P < 0.0001)[11]. However, our «pre-treatment» washout was also inferior (1 *vs* 2 weeks), and likewise the mean dose of RenaGel® was lower in our study (2.8 ± 0.6 g daily *vs* 5.4 g daily)[11]. Obviously, a higher sevelamer dose would improve our results, but we were constrained by this binder present high price at our country (around € 0.75 / 403 mg tablet).

Block y cols., analysed data from 6,407 patients from the US Renal Data System (USRDS), Case Mix Adequacy Study (CMAS) and the Dialysis Morbidity and Mortality Study Wave 1 (DMMS). They have showed that adjusted relative risk of death for patients with phosphorus level greater than 6.5 mg/dl was 1.27 relative to those with serum phosphorus of 2.4 to 6.5 mg/dl[14]. Although the level of phosphorus achieved at the end of our study was not perfect from this point of view, it was reached in patients with severe secondary hyperparathyroidism.

Our study may be criticised for this short washout period of only one week. In fact, this may be insufficient to eliminate the effect of the former binders. For instance, Chertow[1] on an open-label clinical trial in 192 haemodialysed patients used 2 weeks of binders washout and reached a phosphorus increase of 1.65 ± 1.89 mg/dl (P < 0.0001). We must emphasise, however, that in our patients «pre-treatment» PTHi was significantly higher (714 pg/ml *vs* 287 pg/ml) precluding us from an extended washout period, which would aggravate their severe hyperparathyroidism. Furthermore, a higher «pre-treatment» phosphorus level, by a greater extended binder washout, could only amplify our objective of demonstrating sevelamer binder efficacy.

It was relevant that sevelamer binder response could be estimated in only 4 weeks. The «responder» group, that after the binder washout had a serum phosphorus of 7.2 ± 1.2 mg/dl showed a progressive phosphorus decrease until the 4th week (6.7 ± 1.0 mg/dl; P = 0.04), 8th week (6.1 ± 1.4 mg/dl; P = 0.008) and 12th week (5.6 ± 1.0 mg/dl; P = 0.0002). Age, gender, time on dialysis, aetiology of primary renal disease or baseline PTHi could not predict this «binder-response».

Sevelamer treatment at our study was associated with a increase of serum calcium from 10.0 ± 0.5 mg/dl to 10.5 ± 0.8 mg/dl (p = 0.02) corresponding to a mean change of + 0.5 ± 1.0 mg/dl comparing with the «pre-treatment» values. Calcium may increase with RenaGel® treatment as it was showed in several studies[1, 11, 15]. This increase was explained by Slatopolsky[11] with several factors, such as less precipitation of serum calcium with correction of calcium × phosphate product, improved calcemic response to PTH with phosphate control and increased intestinal calcium absorption caused by phosphate binding of RenaGel®.

Alkaline phosphatase increased by 14.3% (100 ± 30 *vs* 115 ± 36 U/L; P < 0.01) as it was revealed in other studies[1, 10, 15].

The patients' selection criterion for calcium- and aluminum-free phosphate binders is in debate. Our study, performed in a group with severe secondary hyperparathyroidism and good nutrition state (PNA 1.33 ± 0.29; serum albumin 3.9 ± 0.2 g/l) reached some conflictive results. In our perspective, the PTHi stability and the phosphate reduction achieved support the initial selection of this group of patients. It could induce a stoppage on the hyperparathyroidism progression culminating on surgical parathyroidectomy.

RenaGel® treatment induced a reduction of LDL cholesterol from 154 ± 32 mg/dl to 132 ± 25 mg/dl (-23%; P < 0.01) and triglycerides from 219 ± 82 mg/dl to 181 ± 62 mg/dl (p < 0.05). The HDL cholesterol showed a trend to increase from 41.6 ± 7.1 mg/dl to 43.9 ± 10.2 mg/dl (7%; P = NS). The reduction of LDL cholesterol and the relative stability of HDL cholesterol with RenaGel® are very well described on various studies[8,10-11,15]. Altogether, this treatment may be an alternative to HMG-CoA reductase inhibitors and fibric acid derivatives in end-stage renal failure, considering the increased risk of side effects of these medications in this setting[16]. Cardiovascular disease is the most common cause of death among dialysis patients[17] forcing us to consider this new phosphate binder alternative with lipid favourable effects.

Lipoprotein(a) is an independent risk factor for atherosclerotic cardiovascular disease in end stage renal disease[18]. It was also proved that it is consistently elevated in chronic renal failure[19]. On our study the patients had high values of Lipoprotein(a) but RenaGel® treatment failed to induce any improvement (131 ± 149 mg/dl *vs* 134 ± 127 mg/dl; P = NS). However, there is a need for long-term studies of lipid lowering in dialysis patients that should include sevelamer[11]. Until now, there are no other studies that followed the effects of sevelamer on Lipoprotein(a).

In short, RenaGel® was an effective phosphate binder in the majority of our haemodialysis patients with severe secondary hyperparathyroidism. Sevelamer binder-«response» could be predicted after 4 weeks, but we did not find any predictors for that response. The lipid profile improved with the treatment, excluding Lipoprotein(a) stabilization. Selection of patients with severe secondary hyperparathyroidism for RenaGel® use could be proper because of its present high price in our country.

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