original article

Wien Klin Wochenschr (2011) 123: 204–208
DOI 10.1007/s00508-011-1551-1

Printed in Austria

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Sevelamer use and incidence of peritonitis in peritoneal dialysis

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Received October 15, 2010, accepted after revision January 12, 2011, published online March 28, 2011

Sevelamereinnahme und Peritonitisinzidenz bei Peritonealdialyse

Zusammenfassung. *Hintergrund:* Sevelamer, ein nichtkalzium-hältiger Phosphatbinder, der häufig bei chronischem Nierenversagen benutzt wird, ist gehäuft mit dem Auftreten von gastrointestinalen Nebenwirkungen verbunden. Ob Sevelamer allerdings auch ein Risikofaktor für Peritonitis bei Peritonealdialyse (PD)-Patienten ist, ist unklar.

Methoden: Wir führten eine retrospektive Analyse aller PD-Patienten durch ($n = 48$), die zwischen Juni 2003 und Dezember 2009 an unserer Abteilung behandelt wurden. Die Daten umfassten 1200 Patientenmonate und 49 Peritonitisepisoden. Demographische Daten der Patienten, Komorbiditäten, Begleitmedikation, Laborparameter und mikrobiologische Ergebnisse wurden den Krankenakten und der elektronischen Datenbank der Klinik entnommen.

Ergebnisse: Die durchschnittliche Peritonitis-Inzidenzrate betrug 0,50/Patientenjahr. Die Dauer der Peritonealdialyse wurde als Risikofaktor identifiziert. Weder Sevelamergabe im Allgemeinen noch die tägliche Dosis im Speziellen waren mit dem Risiko für Peritonitis assoziiert, auch nicht nach Adjustierung der Analyse.

Schlussfolgerung: Die Behandlung mit Sevelamer ist nicht mit einem höheren Risiko für Peritonitis assoziiert.

Summary. *Background:* Sevelamer, a non-calcium containing phosphate binder often used in end-stage renal disease, is frequently associated with gastrointestinal side effects. However, whether Sevelamer is also a risk factor for peritonitis in patients on peritoneal dialysis (PD) is unclear.

Methods: We performed a retrospective analysis of all patients treated with peritoneal dialysis ($n = 48$) between June 2003 and December 2009 at our institution. Data consisted of 1200 patient months and 49 episodes of peritonitis. Patient demographic data, comorbidities, concomitant medication, laboratory parameters, and microbiology results were obtained from the medical records and from the hospital's electronic database.

Results: The mean peritonitis incidence rate was to 0.50/patient year. An identified risk factor for peritonitis was time on PD. Neither Sevelamer use in general nor the mean daily intake was associated with the risk for peritonitis even after adjustment.

Conclusion: Treatment with Sevelamer is not associated with a higher risk for peritonitis.

Key words: Peritoneal dialysis, peritonitis, Sevelamer, peritonitis incidence, risk factor.

Introduction

Peritoneal dialysis-associated peritonitis still represents a major complication of peritoneal dialysis (PD) being a leading cause of hospitalization [1], catheter loss and technique failure [2], and the second most common cause of death in PD patients [3]. Several clinical and demographic factors have previously been reported to be associated with an increased risk of peritonitis, such as age, female gender, current smoking status, the pre-twin-bag connection system [4], higher BMI and comorbidities like coronary artery disease, diabetes mellitus and chronic pulmonary disease [5, 6].

Several studies suggest a beneficial role of RAAS inhibitors [7, 8], and statins [9] in peritoneal dialysis (PD) patients regarding the risk for peritonitis and in a recent study [10] we found a protective effect of oral active vitamin D. Adjusted for time on PD and serum albumin, vitamin D was associated with an 80% reduced relative risk.

Sevelamer is a calcium-free, aluminum-free phosphate binder that is frequently used to treat hyperphos-

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phatemia in dialysis patients. Hyperphosphatemia plays a role in the development of CKD-MBD and has been associated with increased morbidity and mortality in dialysis patients. Treatment of hyperphosphatemia includes reduction in dietary intake of phosphate, inhibition of intestinal phosphate absorption with phosphate binders, and removal of phosphate with dialysis. Sevelamer hydrochloride taken with meals has been shown to decrease serum phosphorus concentrations in patients who are on dialysis. Sevelamer also decreases serum levels of low density lipoprotein and increases high density lipoproteins in hemodialysis patients [11]. Uncontrolled cross-sectional studies showed a similar benefit for patients on peritoneal dialysis [12].

The most commonly observed adverse reactions in dialysis patients taking Sevelamer are related to the gastrointestinal tract including dyspepsia, diarrhea, nausea, and constipation. Data on side effects of Sevelamer specifically in PD patients are scarce. In a study by Evenepoel and colleagues' treatment with Sevelamer was not associated with a significant increase in the risk of peritonitis, although peritonitis occurred in 11% of the patients in the Sevelamer group and in 4% of the patients on calcium-containing phosphate binders [13]. However, in this study peritonitis rate was not a predefined endpoint and the rate was within the expected range in both groups. Therefore, the association between treatment with Sevelamer and the risk for peritonitis in PD patients remains unclear. It could be hypothesized that a higher rate of diarrhea and constipation might increase the risk of peritonitis caused by gram-negative microorganisms due to transmural migration of bacteria, hence it is recommended to avoid constipation in PD patients [14, 15].

The aim of our study was to analyze a potential association between the use of Sevelamer and a higher risk for peritonitis in PD patients at our institution.

Patients, materials, and methods

Patients

Medical records of prevalent ($n = 6$) and incident patients ($n = 42$) of our PD unit were reviewed between June 1st, 2003 (when Sevelamer treatment was introduced in Austria) and December 31st, 2009. The study was limited to adults who (1) were stable on PD for >90 days, (2) did not interrupt PD for >90 days, and (3) did not experience an episode of peritonitis during the first month of the study to prevent a bias resulting from relapsing episodes of peritonitis (one patient was excluded). The diagnosis of an episode of peritonitis was established when 2 of the following findings were present: (a) abdominal pain, (b) cloudy effluent and/or (c) an effluent cell count of WBC > 100/µl with at least 50% neutrophils. Laboratory parameters were collected at baseline. Once a patient received Sevelamer before the first episode of peritonitis, the patient remained in the Sevelamer cohort for all further analyses (i.e. in an intention-to-treat manner). In 11 patients we could not define the exact dose of Sevelamer due to a non-fixed dosage. These patients were excluded from all dose-related analyses. For the time-dependent analysis patients were included in the analysis until they reached an endpoint, i.e. (1) an episode of peritonitis, (2) transfer to HD, (3) kidney transplantation, (4) death, (5) lost to follow-up.

Statistical analysis

Baseline characteristics are given as means (± standard deviation) and as median (minimum–maximum) where appropriate. Two-tailed *t*-test, Mann–Whitney U-test and Chi-square (χ^2) test, respectively, with a confidence interval of 95% were used. The frequency of PD-associated peritonitis was calculated as episodes per patient year. We used Kaplan–Meier curves and calculated the logrank test to examine time free of peritonitis in patients with and without Sevelamer. Unadjusted and adjusted Cox proportional hazard models were used to further examine the impact of Sevelamer on peritonitis. The analysis was performed using IBM SPSS Statistics 18.0. This study has been approved by the Institutional Review Board of the Medical University of Innsbruck.

Table 1. Comparison of Patients with and without an episode of Peritonitis

	No peritonitis	Peritonitis	*p*-value
Demographic and clinical data			
Male/Female (*n*)	14/8	14/12	0.493
Age (years)	54.1 ± 15.4	49.1 ± 13.2	0.225
BMI (kg/m²)	23.0 ± 3.8	23.9 ± 4.0	0.422
Time on PD (months)	14.4 ± 11.8	34.0 ± 17.8	0.001
Comorbidities† (*n*)			
Diabetes	6	3	0.267
Myocardial infarction	2	3	1.000
Cardiomyopathy	3	0	0.089
Cerebral vascular disease	2	2	1.000
Peripheral vascular disease	1	2	1.000
Primary renal disease† (*n*)			
Glomerulonephritis	9	5	0.100
Diabetic nephropathy	4	3	0.687
PCKD	1	3	0.614
Other (e.g., interstitial nephritis)	5	13	0.052
Unknown	3	2	0.649
Type of PD† (*n*)			
CAPD	20	21	0.429
APD	0	4	0.114
Both	2	1	0.587
Laboratory parameters at baseline			
Albumin (mg/dl)	3222 ± 652	3457 ± 556	0.184
Hemoglobin (g/l)	110 ± 16	111 ± 14	0.839
Ferritin (ng/ml)	135.5 (12–1329)	127 (23–611)	0.959
Calcium (mmol/l)	2.19 ± 0.25	2.26 ± 0.25	0.332
Phosphate (mmol/l)	1.97 ± 0.69	2.08 ± 0.62	0.553
Parathormone (ng/l)	252.9 ± 185.7	281.6 ± 220.9	0.631
Comedication† (*n*)			
Calcium-based phosphate binders	16	20	0.738
Sevelamer	18	19	0.473
Oral active vitamin D	18	20	0.735
Statins	12	16	0.624
Immunosuppression	8	8	0.682
RAAS inhibitors	17	17	0.367
Mean dose of Sevelamer (g/d)	2.39 ± 1.30	2.65 ± 1.23	0.615
Cum. dose of Sevelamer (g)	380.6 ± 359.7	734.7 ± 782.9	0.159

APD automated PD; *BMI* Body mass index; *CAPD* continuous ambulatory PD; *Cum.* cumulative; *HD* hemodialysis; *PCKD* polycystic kidney disease; *PD* peritoneal dialysis; *RAAS* renin–angiotensin–aldosterone system.
†Patients with "yes" conditions presented.

Table 2. Sevelamer: baseline laboratory and clinical data

Variable	Sevelamer		*p*-value
	No	Yes	
Patients (*n*)	11	37	–
Age (years)	56.3 ± 13.0	49.9 ± 14.5	0.196
BMI (kg/m²)	24.5 ± 5.5	23.1 ± 3.3	0.454
Time on PD (months)	33.7 ± 25.7	22.4 ± 14.7	0.191
Time to 1st peritonitis (months)	16.6 ± 21.6	18.0 ± 11.9	0.828
Peritonitis episodes/py	0.59	0.45	–
Prevalent patients (*n*)	2	4	0.609
Albumin (mg/dl)	3147 ± 435	3409 ± 642	0.212
Hemoglobin (g/l)	113 ± 17	110 ± 14	0.508
Ferritin (ng/ml)	119 (15–332)	136 (12–1329)	0.358
Calcium (mmol/l)	2.37 ± 0.23	2.19 ± 0.24	0.037
Phosphate (mmol/l)	1.90 ± 0.46	2.07 ± 0.69	0.463
Parathormone (ng/l)	227.1 ± 172.6	280.7 ± 212.9	0.450
Oral active vitamin D (*n*)	10	28	0.416

BMI Body mass index; *PD* peritoneal dialysis; *py* patient year

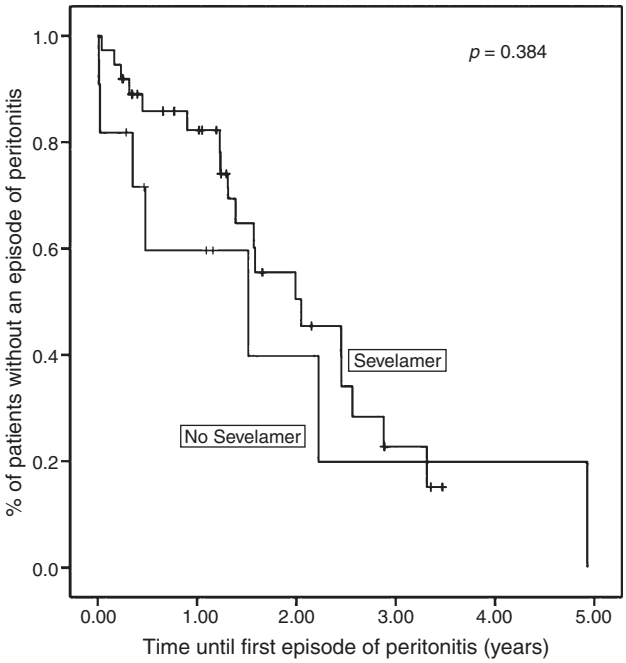

Fig. 1. Kaplan–Meier analysis of peritonitis-free time on peritoneal dialysis

Results

We compared demographic and clinical data between patients with and without an episode of peritonitis to identify confounding factors (Table 1). There was a significant difference in total time on PD (14.4 ± 11.8. *vs.* 34.0 ± 17.8 months; $p = 0.001$).

Table 2 compares the patients according to whether they were on Sevelamer treatment at any timepoint before reaching the endpoint (in an intention-to-treat manner). Serum calcium at baseline was higher in the cohort not treated with Sevelamer (2.37 ± 0.23 *vs.* 2.19 ± 0.24; $p = 0.037$).

There was no significant difference with regard to the incidence of peritonitis between the groups ($p = 0.384$; Fig. 1). Prevalent patients whose PD treatment started before the time of the study period, i.e. before Sevelamer was prescribed at our PD unit, did not differ from incident patients who began PD after June 1st, 2003 in terms of risk for the first episode of peritonitis (data not shown).

In an unadjusted Cox proportional hazard model (Table 3), hazard ratios for the risk for peritonitis did not differ significantly between the two groups. Adjusted for time on PD, hazard ratios did not differ, either.

We established two different dose groups (Fig. 2), which were defined as "≤2400 mg/day" ($n = 13$) and ">2400 mg/day" ($n = 12$) (corresponding to the mean in our cohort). There were no significant differences between patients who were never treated with Sevelamer ($n = 12$), patients who received ≤2400 mg/day ($n = 13$), and those who received >2400 mg/day ($n = 12$) with regard to the risk for

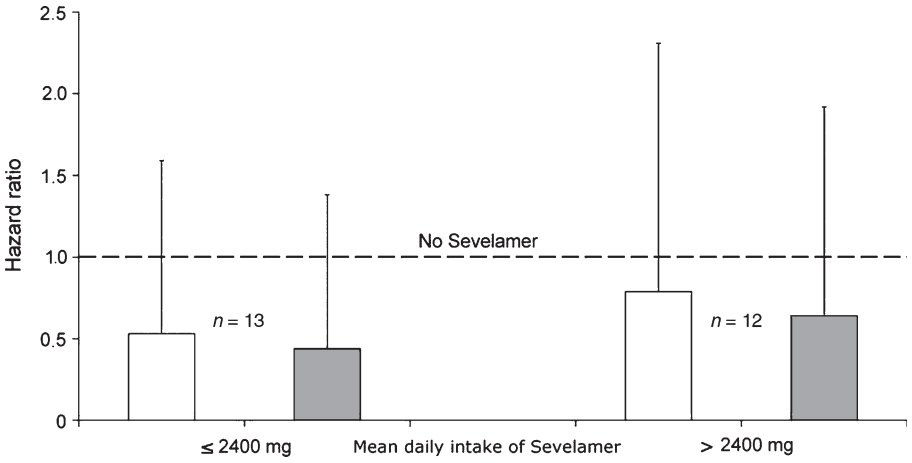

Fig. 2. Hazard ratio for PD-associated peritonitis by mean daily intake of Sevelamer. White bars: Unadjusted risk. Grey bars: Risk adjusted for time on PD

Table 3. Cox regression hazard model: Sevelamer and the risk for peritonitis

	Hazard ratio	95 % CI
Unadjusted model		
Sevelamer		
No	1.00	–
Yes	0.67	0.26–1.67
Adjusted model		
Sevelamer		
No	1.00	–
Yes	0.55	0.21–1.42

CI confidence interval.

Table 4. Comparison of identified microorganisms in peritonitis episodes of patients with Sevelamer ($n = 7$) and patients without sevelamer ($n = 19$)

	Sevelamer	No sevelamer	*p*-value
Gram-positive (*n*)	20	10	0.428
Gram-negative (*n*)	4	3	0.366
No germ identified (*n*)	5	3	0.264
Other (e.g. Candida) (*n*)	1	2	0.507
Unknown (*n*)	2	0	0.392

peritonitis (HR 0.53; 95% CI 0.18–1.59 *vs.* HR 0.79; 95% CI 0.27–2.31), even after adjustment for time on PD (HR 0.44; 95% CI 0.14–1.38 *vs.* HR 0.64; 95% CI 0.21–1.92).

Further analysis of microorganisms causing peritonitis in patients with and without Sevelamer revealed no significant differences (Table 4). Neither the rate of gram-positive nor of gram-negative peritonitis was significantly higher in the group treated with Sevelamer. Furthermore, there were no differences in the number of peritonitis episodes associated with exit-site or tunnel infection ($p = 0.389$; data not shown).

Discussion

In our study we did not detect any significant difference in the peritonitis rates between PD patients treated with Sevelamer and those treated with calcium containing phosphate binders. It has been postulated that PD patients may be expected to have a greater sensitivity to gastrointestinal adverse effects than HD patients due to abdominal cavity loading with dialysate. In the only controlled study analyzing the efficacy and safety of Sevelamer in PD patients, gastrointestinal side effects and peritonitis occurred more often in the Sevelamer group than in the calcium acetate group, although the difference was not statistically significant [13]. Peritonitis rate in patients treated with Sevelamer was in the expected range which has been previously reported in the literature. Furthermore, in a study by Kahvecioglu et al. it was shown that gastrointestinal complaints were not different between HD and PD patients [16]. Slightly heterogenous results between the study by Evenopoel et al. and our study could be explained by differences in study design (prospective *vs.* retrospective), the duration of the study (12 weeks *vs.* 1200 patient months), the size of the cohorts (143 patients *vs.* 48 patients), and the center bias (multi-center *vs.* single-center). In addition, results of our study might be biased by indication because serum calcium levels differed significantly between patients treated with Sevelamer and patients not treated with Sevelamer.

It can be further hypothesized that patients treated with Sevelamer might be at higher risk for peritonitis caused by transmural migration of bacteria of enteric origin (i.e. gram-negative infections). In our study neither treatment with Sevelamer was associated with a higher rate of gram-negative peritonitis nor was there any difference in the rate of catheter-related peritonitis episodes between the groups. In the study by Evenepoel et al. no data on the causative microorganisms were published.

In a former study by our group [10], oral active vitamin D has been identified as a protective factor in terms of preventing the first episode of peritonitis. Also in the present study patients who were treated with oral active vitamin D had a significantly lower risk for peritonitis than patients not treated with vitamin D ($p = 0.036$).

One important goal in end-stage renal disease patients is to maintain serum phosphate in the range recommended from the National Kidney Foundation (1.13–1.78 mmol/l; [17]). Elevated serum phosphate contributes to the high morbidity and mortality observed in these patients [18]. Sevelamer treatment in PD patients seems to be as efficacious as in HD patients in maintaining serum phosphate and calcium-phosphate product within the target range, but efficacy appears to be less in those patients with severe hyperparathyroidism [19]. In [12], 61% of PD patients treated with Sevelamer showed adequate control of serum phosphate.

In [20] and also in [19] serum PTH-levels were unchanged during the study. Possible explanations could be the loss of vitamin D-binding protein and 1,25-dihydroxycholecalciferol throughout the peritoneal fluids [21], and the vitamin D-depletive effect of Sevelamer as a bile salt binder, which may decrease fatty acid intestinal absorption and therefore interrupt the enterohepatic cycle of vitamin D [22], which may lead to less suppressive action of vitamin D on parathyroid glands. Katopodis et al. [20] studied a cohort of 30 PD patients in an open-label, randomized crossover study, comparing treatment with Sevelamer and aluminum hydroxide. Sevelamer decreased total cholesterol by about 10% and LDL-Cholesterol by about 20%. HDL-Cholesterol remained statistically unaffected. Although aluminum hydroxide has also a strong affinity to bile acids, they did not observe any beneficial effect of it on lipid parameters. In another study, significant decreases in total cholesterol, LDL-cholesterol, and non-HDL-cholesterol were observed in PD patients treated with Sevelamer but not in patients treated with calcium acetate [13]. HDL-cholesterol did not change from baseline in either group. Also in [12] and [19] the authors could show a beneficial effect of Sevelamer on total cholesterol and LDL-cholesterol. Whether these phosphate- and lipid-lowering properties

of Sevelamer will also translate into enhanced survival has yet to be determined.

Summarizing the results from our study and from others we conclude that treatment with Sevelamer is not associated with a higher risk of peritonitis in PD patients.

Conflict of interest

We declare that the results presented in this paper have not been published previously in whole or part. This study has been supported by an unrestricted research grant from Genzyme to GM.

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