RISK FACTORS AND CONSEQUENCES OF HYPERALUMINEMIA IN A PERITONEAL DIALYSIS COHORT

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◆ **Background:** Widespread Al toxicity is unusual today. In 2005, Canadian peritoneal dialysis (PD) centers reported widespread hyperaluminemia in patients using dialysates from one specific manufacturer. Our objectives were to evaluate risk factors related to Al accumulation and to assess its clinical consequences in patients from 2 centers.

◆ **Methods:** A retrospective closed cohort study was conducted in patients treated with PD in May 2005. A multivariate linear regression model was constructed to identify variables associated with a higher serum Al level in the exposed group at the moment of solution change. Using appropriate statistical methods, anemia and bone metabolism parameters were compared between the exposed and unexposed groups. Time to first peritonitis was estimated by the Kaplan–Meier method.

◆ **Results:** The study cohort included 87 Al-exposed patients and 95 unexposed patients. In the exposed group, serum Al at the moment of solution change was influenced by the length of exposure to Al-containing dialysates and by PD creatinine clearance; serum Al was inversely correlated with renal creatinine clearance. No consequences of Al accumulation were observed. No difference was observed in the time to first peritonitis between patients who switched manufacturers and those who remained with the original manufacturer.

◆ **Conclusions:** Our results suggest that hyperaluminemia is directly related to the length and extent of exposure to Al-containing dialysates; residual renal function is protective against Al accumulation. Because the problem was detected rapidly, no clinical consequences of hyperaluminemia were observed in the study cohort.

KEYWORDS: Aluminum; toxicity; bone disease; anemia; intoxication.

Aluminum toxicity has long been a prevalent concern in the end-stage renal disease population. Toxicity because of excess Al can induce low-turnover osteomalacia, low levels of parathyroid hormone, anemia, microcytosis, and increased erythropoietin requirements (1,2). Such manifestations were commonly reported in the 1970s and 1980s in patients inadvertently exposed to low-level Al content in dialysates or receiving chronic therapy with Al-containing phosphate binders (1,3–7). Symptoms that are more acute and apparent, such as encephalopathy and seizures, have historically been described with overt contamination of dialysate water (8,9). With better preparation of dialysates and the advent of Al-free binders, Al-related disease is now considered much rarer.

In 2004 – 2005, several Canadian peritoneal dialysis (PD) centers noted increasing serum Al levels during yearly routine monitoring in patients using Fresenius PD systems (Fresenius Medical Care North America, Waltham, MA, USA). Investigation eventually attributed the change to high Al content (approximately 1.3 $\mu\text{mol/L}$) in dialysates manufactured by Fresenius Canada. An earlier longitudinal analysis identified January 2004 as the moment of significant initial contamination (10). All Canadian dialysis units were immediately notified. In June 2005, affected patients were proposed the choice of either changing manufacturers [to Baxter Healthcare (Deerfield, IL, USA) or Gambro Lundia (Lund, Sweden)] or receiving Al-free dialysates from Fresenius.

The main objectives of the present study were to evaluate risk factors for Al accumulation, to identify the clinical consequences of Al toxicity, and to verify whether an enhanced risk of peritonitis was associated with a precipitous switch in dialysis systems.

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METHODS

This study was conducted in 2 Canadian adult care hospitals: Verdun Hospital, a 300-bed community hospital located in Montreal, Quebec, and Scarborough Hospital, a 600-bed community hospital in Toronto, Ontario.

A retrospective closed cohort analysis was conducted among all patients treated with PD at both centers in May 2005. Patient information and lab results were extracted from computerized records and patient charts. The ethics committee of both hospitals were notified of the study. Given that no direct patient contact was required for study purposes, the need for written informed consent was waived.

STATISTICAL ANALYSES

Using appropriate statistical methods (means by the Student t-test, medians by the Wilcoxon rank sum test, and proportions by the chi-square test), we compared patient demographics and laboratory data between the exposed and unexposed groups. Curves representing time to first peritonitis were analyzed using the Kaplan–Meier method and compared using the log-rank test. A value of $p < 0.05$ (2-sided) was considered statistically significant.

To identify factors influencing serum Al in the exposed group, we performed a linear regression analysis evaluating the relationship of various variables with serum Al at the moment of the solution change. The variables evaluated on univariate analysis were age, sex, weight, serum albumin, serum transferrin, type of PD, PD creatinine clearance (obtained using a standardized peritoneal equilibration test), number of daily PD exchanges, daily PD influx volume, protein content in dialysate, daily urine output, renal creatinine clearance, and total time on PD before and after significant Al exposure (identified as January 2004). Because a highly skewed distribution for the residuals of the renal creatinine clearance variable, a natural logarithmic transformation was performed to normalize the distribution. A multivariate linear regression model was constructed using variables identified from the univariate analysis as influencing serum Al at the moment of solution switch ($p < 0.2$). The presence of interaction terms was evaluated. Based on *a priori* knowledge, no variable was forced in the model. A stepwise selection was used with p value of less than 0.1 for entry and less than 0.05 for removal. Statistical analyses were performed using the SAS software application (version 9.1: SAS Institute, Cary, NC, USA).

RESULTS

PATIENT CHARACTERISTICS

Table 1 summarizes the characteristics of the patients. Before the solution change, 87 patients performed PD using dialysates from Fresenius (“exposed group”) and 95 used solutions from Gambro or Baxter (“unexposed

TABLE 1
Demographics of Peritoneal Dialysis (PD) Patients
Exposed and Unexposed to Excess Al at the
Time of Solution Change, May 2005

Variable	Group ^a		<i>p</i> Value
	Exposed	Unexposed	
Patients (<i>n</i>)	87	95	
Sex [<i>n</i> (%) men]	39 (44.8)	48 (50.5)	0.5
Age (years)			
Mean	61.9	64.4	0.3
95% CI	58.7 to 65.2	61.3 to 67.6	
Time on PD (months)			
Median	21.2	31.1	0.01
Range	11.6–38.7	17.9–49.4	
Type of PD [<i>n</i> (%)]			
CAPD	47 (54.0)	54 (56.8)	0.7
CCPD	24 (27.6)	28 (29.5)	
NIPD	16 (18.4)	13 (13.7)	
Daily exchanges (<i>n</i>)			
Median	4.5	4.6	0.3
Range	4.0–5.0	4.0–5.0	
Daily influx volume (L)			
Median	10.0	10.0	0.9
Range	8.0–10.0	8.0–12.0	
Daily urine volume (L)			
Median	0.60	0.50	0.8
Range	0.15–1.10	0.27–1.10	
CCr (mL/min)			
Peritoneal			
Mean	4.94	5.05	0.5
95% CI	4.03 to 5.74	4.01 to 5.97	
Renal			
Median	3.77	3.63	0.7
Range	0.95–6.96	1.14–6.87	
Serum Al before PD (μmol/L)			
Mean	0.19	0.14	0.1
95% CI	0.08 to 0.29	0.09 to 0.19	

CI = confidence interval; CAPD = continuous ambulatory PD; CCPD = continuous cycling PD; NIPD = nocturnal intermittent PD; CCr = creatinine clearance.

^a For medians, “range” is the lower and upper interquartile range.

group"). Age, sex, type of PD, number of daily exchanges, daily influx volume, and PD and renal creatinine clearances were similar in both groups. The only statistically different variable was a longer time on dialysis in the unexposed group than in the exposed group (31.1 months vs 21.2 months, $p = 0.01$).

VARIABLES INFLUENCING SERUM ALUMINUM

The univariate linear regression analysis identified several variables associated with a higher serum Al level at the moment of the solution switch in the exposed group ($n = 67$): age, type of PD, PD creatinine clearance, number of daily PD exchanges, daily PD influx volume, daily urine output, renal creatinine clearance (with natural logarithmic transformation), total time on PD before significant Al exposure, and time on PD since the beginning of significant Al exposure (Table 2).

The final multivariate model identified 3 independent variables influencing serum Al in the exposed group ($n = 63$): renal creatinine clearance (within the patients' range of 0.1 – 39 mL/min), PD creatinine clearance, and time on PD since significant Al exposure (Table 3). No interaction terms were identified. Assuming that the other independent variables remain

constant, the multivariate linear regression model is interpreted as follows:

- For every doubling of renal creatinine clearance, a decrease of 0.16 $\mu\text{mol/L}$ in the mean maximal serum Al is observed.
- For every month of exposure to Al-contaminated dialysate, an increase of 0.07 $\mu\text{mol/L}$ in the mean maximal serum Al is observed.
- For every increase of 1 mL/min in PD creatinine clearance, an increase of 0.22 $\mu\text{mol/L}$ in the mean maximal serum Al is observed.

The proportion of the variation in the dependent variable (maximal serum Al) accounted for by the 3 explanatory variables was 47.7% (model adjusted R^2).

CONSEQUENCES OF ALUMINIUM CONTAMINATION

At the time of PD solution change, all studied outcomes related to bone metabolism and anemia were similar in the two groups, except for a lower reticulocyte count in the contamination group (which was also present before initiation of dialysis, Table 4). No encephalopathy or newly diagnosed dementia was reported in either center. No patient required deferoxamine treatment or switch to high-flux daily dialysis. No difference in the time to first peritonitis was observed

TABLE 2
Univariate Analysis of Variables Potentially Influencing Serum Al in the Exposed Group of Peritoneal Dialysis (PD) Patients ($n = 67$)

Variable	β Coefficient	SE of coefficient	95% CI	p Value
Age (years)	-0.01	0.006	-0.02 to 0.002	0.08
Sex (male)	-0.26	0.18	-0.60 to 0.09	0.2
Weight (kg)	-0.003	0.005	-0.01 to 0.01	0.5
Serum albumin (g/L)	-0.03	0.25	-0.08 to 0.02	0.3
Serum transferrin (g/L)	-0.11	0.27	-0.63 to 0.42	0.7
Type of PD (CAPD vs CCPD or NIPD)	-0.53	0.17	-0.86 to -0.20	0.002
PD CCr (mL/min)	0.24	0.07	0.11 to 0.37	0.0006
Daily exchanges (n)	0.24	0.11	0.15 to 0.46	0.04
Daily influx volume (L)	0.15	0.04	0.07 to 0.22	0.0003
Effluent protein content (g/L)	-0.007	0.02	-0.04 to 0.03	0.7
Daily urine output (L)	-0.39	0.15	-0.39 to -0.10	0.01
Natural log of renal CCr	-0.26	0.07	-0.39 to -0.12	0.0004
Timing of significant Al exposure (months)				
Time on PD before ^a	0.02	0.006	0.01 to 0.03	0.001
Time on PD after ^a	0.08	0.02	0.05 to 0.12	<0.0001

SE = standard error; CI = confidence interval; CAPD = continuous ambulatory PD; CCPD = continuous cycling PD; NIPD = nocturnal intermittent PD; CCr = creatinine clearance.

^a Identified as January 2004.

TABLE 3
Multivariate Analysis of Variables Influencing Serum Al in the Exposed Group ($n = 63$)^a

Independent variable	β Coefficient	SE of coefficient	95% CI	<i>p</i> Value
Intercept	0.09	0.33	-0.57 to 0.74	0.8
Natural log of renal CCr	-0.23	0.06	-0.35 to -0.12	0.0001
Peritoneal CCr (mL/min)	0.22	0.05	0.11 to 0.32	0.0002
Time on PD (months) ^b	0.07	0.02	0.04 to 0.10	<0.0001

SE = standard error; CI = confidence interval; CCr = creatinine clearance; PD = peritoneal dialysis.

^a Final multivariate linear regression model: serum Al (at the time of solution switch) = $0.09 - 0.23$ (natural log of renal CCr) + 0.22 (peritoneal CCr) + 0.07 (time of significant exposure) + interindividual variability.

^b Since the start of estimated significant Al exposure (identified as January 2004).

TABLE 4
Patient Outcomes in Peritoneal Dialysis (PD) Patients Exposed and Unexposed to Excess Al at the Moment of Solution Change, May 2005

Variable ^a		Group		<i>p</i> Value
		Exposed ($n=87$)	Unexposed ($n=95$)	
Serum Al ($\mu\text{mol/L}$)	Mean	1.77	0.13	<0.001
	95% CI	1.39 to 2.23	0.09 to 0.18	
Hemoglobin (g/L)	Mean	118.2	116.3	0.3
	95% CI	115.6 to 120.8	113.6 to 119.0	
Hematocrit (%)	Mean	0.35	0.35	1.00
	95% CI	0.35 to 0.36	0.35 to 0.36	
Mean corpuscular volume (fL)	Mean	91.4	92.3	0.4
	95% CI	90.3 to 92.6	90.7 to 93.9	
Reticulocyte count ($10^9/\text{L}$)	Median	62.0	75.0	0.01 ^b
	Range	44.0–79.0	53.0–95.0	
Transferrin (g/L)	Mean	2.03	1.98	0.4
	95% CI	1.96 to 2.11	1.90 to 2.06	
Transferrin saturation (%)	Median	0.24	0.21	0.1
	Range	0.18–0.32	0.18–0.28	
Ferritin (g/L)	Median	177.0	226.0	0.1
	Range	86.0–348.0	137.5–394.0	
EPO dose (U/week) ^c	Median	4000	6000	0.1
	Range	2000–8000	3000–12000	
Albumin (g/L)	Mean	31.1	30.6	0.5
	95% CI	30.2 to 31.9	29.4 to 31.7	
PTH (pmol/L)	Median	22.7	30.5	0.4
	Range	11.2–49.6	14.8–41.5	
Calcium (mmol/L)	Mean	2.46	2.43	0.2
	95% CI	2.43 to 2.49	2.39 to 2.46	
Phosphorus (mmol/L)	Mean	1.54	1.55	0.8
	95% CI	1.43 to 1.63	1.46 to 1.64	

CI = confidence interval; EPO = erythropoietin; PTH = parathyroid hormone.

^a "Range" is the lower and upper interquartile range.

^b Count was also lower in the contaminated group before PD initiation ($51 \times 10^9/\text{L}$ vs $69 \times 10^9/\text{L}$, $p = 0.001$).

^c For patients taking darbepoetin alpha, the weekly dose in micrograms was multiplied by 200 to convert to the equivalent weekly erythropoietin dose.

Figure 1 — Time to first peritonitis in peritoneal dialysis (PD) patients who changed (dotted line) and did not change (solid line) from Fresenius solutions (Fresenius Medical Care North America, Waltham, MA, USA) to solutions from another manufacturer (Baxter Healthcare Corporation, Deerfield, IL, USA; or Gambro Lundia, Lund, Sweden). Each dot represents a censored patient who exited PD (either to transplantation, hemodialysis, or death) and who did not develop peritonitis.

between patients who switched manufacturers and those who stayed with Fresenius (Figure 1, $p = 0.2$).

DISCUSSION

In important exposures, Al is potentially toxic to humans. Given that Al is eliminated mainly by the kidneys, patients with end-stage renal failure depend on dialysis to remove excess Al. Historically, significant Al toxicity in this population has been related to the use of Al-base phosphate binders (3), contamination of dialysate (7), and more rarely, defective dialysis apparatus (8).

Our analysis showed that higher Al levels in the exposed group were inversely associated with renal creatinine clearance and positively associated with time on PD since January 2004 and with PD creatinine clearance. All those variables were highly significant.

Significant residual renal function is known to be protective against Al accumulation, permitting removal of approximately 2 μmol daily in chronic kidney disease patients (3,11–15). Furthermore, the relationship was found to be logarithmic: that is, small increments in renal function (above 0.1 mL/min) had a major effect on serum Al. That finding is similar to findings in previous reports (3,13).

Patients who had a higher PD creatinine clearance also had a higher maximal serum Al. This paradoxical result is likely related to exposure to a larger Al burden: that is, the more dialysate used, the higher the PD creatinine clearance and the higher the exposure to contaminated bags. The PD creatinine clearance was found to be a

significant independent factor in serum Al, but the daily PD influx volume was not. Because these variables are closely related (influx volume directly influences PD clearance), it is not surprising that we observed high colinearity between them. Daily PD influx volume seems to explain most of the effect measured by PD creatinine clearance, but other hypotheses, such as peritoneal membrane transport of Al, are also possible.

Time spent on PD since January 2004 simply reflects more prolonged exposure to Al-contaminated solutions.

Symptoms of Al exposure include bone pain, muscle weakness (16), and change in mental status (8). Signs of Al exposure include anemia (17), higher erythropoietin dose (18), microcytosis (1,17), lower ferritin levels (18,19), hypoparathyroidism (20), hypercalcemia (20), and hyperphosphatemia (1,18). Aside from a lower reticulocyte count (which was present before PD initiation, and therefore before Al exposure), none of the foregoing signs or symptoms were observed in the exposed group at the moment of solution change. Despite the extensive tissue distribution and half-life of Al (14), we suspect that Al exposure in our patients was not severe or prolonged enough to lead to significant clinical sequelae. Had the problem gone unnoticed, patients would undoubtedly have continued to accumulate Al with serious clinical effects. Alternatively, earlier signs of Al toxicity could have been uncovered with more invasive investigation such as bone biopsy (16) or central nervous system testing; however, such tests were not performed because no patient in our cohort had a serum Al level above 3.7 $\mu\text{mol/L}$ (1,21). Still, early metabolic histology changes can be seen in patients with serum levels as low as 1.5 $\mu\text{mol/L}$ (22).

Treatment of Al toxicity includes deferoxamine and high-flux daily dialysis, but in asymptomatic patients with serum Al levels below 2.2 $\mu\text{mol/L}$, simple observation appears sufficient (23,24), especially considering the potential side effects of deferoxamine.

Our results suggest that low-level Al exposure does not cause overt clinical toxicity in a PD cohort. Although our work requires confirmation by other studies, we postulate that short-term exposure to Al-based phosphate binders might be similarly innocuous if used appropriately, possibly more so when the Al content of dialysate is negligible, permitting removal of exogenously absorbed Al, an elimination option that was not available to the patients in the present study.

There was a concern that patients who precipitously changed dialysis systems might be at higher risk of peritonitis because of difficulties in learning the intricacies of a new PD technique. Fortunately, increased peritonitis was not observed in our study, suggesting

that patients who need to change manufacturers quickly (for example, because of product recall or contamination) can do so safely. However, we cannot exclude the possibility that the present analysis was underpowered and potentially biased, given that the patients themselves decided on their choice of manufacturer. Incidentally, information bias appears minimal, given that all data were retrieved from computerized databases. Confounding was handled by the multivariate modeling when feasible.

CONCLUSIONS

Our study confirms that, in a context of Al-contaminated dialysate, patients who had more extensive exposure to Al and lower residual renal clearance also had a higher maximal serum Al. Although Al can affect hematopoietic and skeletal systems, no clinical consequences were detected in this large cohort of patients with Al accumulation, although this lack of consequences can be confirmed only by more sensitive testing.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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