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Chemical peritonitis associated with high dialysate acetaldehyde concentrations

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Abstract

Background. During the standard heat sterilization process of lactate-buffered peritoneal dialysis (PD) solutions, glucose degrades to form compounds called glucose degradation products such as acetaldehyde, formaldehyde, or glyoxal. Despite evidence that these products may be responsible for some *in vitro* cytotoxic effects induced by commercially available PD fluids, data on their acute or chronic effects on the human peritoneum is scarce.

Subjects and methods. This case presentation is based on an observation of 21 aseptic peritonitis cases of unknown aetiology. All cases appeared within one month in a university hospital PD unit that had a peritonitis rate of 1 episode/26 patient months and 55 active patients on CAPD. Acetaldehyde level in the bags was assayed by gas chromatography.

Results. Twenty-one patients presented with signs of peritonitis including cloudy dialysate and abdominal tenderness with additional abdominal pain in 11 patients and vomiting in one. In all cases, cultures and Gram stains were negative for micro-organisms. Fever was not observed in any patient. Average dialysate white blood cell count was 1795/mm^3. All patients were free of intraperitoneal medication when symptoms appeared. Patients were using PD solutions from a newly established domestic production plant. Apparently all patients with symptoms of peritonitis used bags with the same lot number and the solution in the bags appeared to be darker in colour than that in bags with other lot numbers. Chemical analysis of the unused PD solution samples revealed acetaldehyde levels of 17–20 p.p.m. in bags containing darker solution, which is very high compared with the usual acetaldehyde level of 6 p.p.m. in heat-sterilized PD solutions.

Conclusions. Based on the above findings, we hypothesize that higher levels of acetaldehyde and possibly other glucose degradation products may have been an aetiological factor in these 21 cases of chemical peritonitis. Our observation suggests that acetaldehyde, in concentrations 3–4 times higher than the usual level in commercially available PD solutions, may induce acute sterile peritonitis in CAPD patients.

Keywords: acetaldehyde; chemical peritonitis, dark dialysate; glucose degradation products; peritoneal dialysis

Introduction

During chronic peritoneal dialysis (PD), the peritoneum is continuously exposed to various insults mostly originating from non-physiological nature of the PD procedure itself and the bioincompatibility of the PD solutions. Information based on peritoneal biopsies and other work, showed that there were signs of serious structural damage [1,2] and also evidence of two active processes in chronic PD modalities: continuous mesothelial injury and continuous mesothelial regeneration [3]. *In vivo* studies with blood and peritoneal cells indicate that hyperosmolality [4], low pH [5,6], low pH and lactate [7,8], lactate [8], and/or glucose degradation products [9] may be responsible for the cytotoxicity of PD fluids. During heat sterilization process of lactate-buffered PD solutions, when the solution pH is 5, heat-induced degradation of glucose has been reported to be minimum [10]. Higher solution pH, lower temperature, and longer sterilization time during the manufacturing process may result in increased production of glucose degradation products like acetaldehyde, 5-hydroxymethyl-2-furfural, formaldehyde, glyoxal, 2-furaldehyde, methylglyoxal, and some unidentified yet biologically active compounds [10–13]. This breakdown process is also called 'caramelization' and may give the fluid a caramel-like, darker, yellow-brown colour. It has also been reported that towards the end of their shelf life commercial PD fluids may contain more irritant glucose metabolites and may induce abdominal pain and reversible loss of ultrafiltration [14,15]. Besides abdominal pain and possible temporary loss of ultrafiltration, there is no

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proven report of any acute or chronic side-effects that may be directly linked to glucose breakdown products. This report of 21 chemical peritonitis cases may be the first clinical evidence that glucose degradation products may cause serious acute side-effects in chronic PD patients.

Subjects and methods

This observation was carried out between 15 October 1996 and 18 November 1996. All 21 end-stage renal failure patients in this report (nine female, 12 male; mean age 48 ± 12 years) had been on continuous ambulatory PD (CAPD) treatment under medical supervision at Akdeniz University Medical School, Department of Medicine, Division of Nephrology, Peritoneal Dialysis Unit. CAPD was performed with a double-bag disconnect PD system. Principal characteristics of the patients are shown in Table 1. Among 55 CAPD patients who had been followed by our PD outpatient clinic by that time, all 21 presented with signs and symptoms of peritonitis, including cloudy dialysate, abdominal tenderness with additional abdominal pain in 11 patients, and vomiting in one. Fifteen episodes accumulated during the week of 18–25 October 1996. Their CAPD regimen was four 2-l exchanges with 1.36/2.27/1.36/3.86% dextrose concentrations in 13 patients, 1.36/2.27/2.27/3.86% dextrose concentrations in four patients, 2.27/2.27/2.27/3.86% dextrose concentrations in two patients, and 2.27/3.86/2.27/3.86% dextrose concentrations in two patients. Mean dialysate white blood cell (WBC) count was 1795/mm^3 (200–9700/mm^3). Aerobic cultures were carried out by injecting 10 ml dialysate samples into two BacT/Alert (Organon Teknica Corp., Durham, NC, USA). Samples were incubated in an automatic blood culture system and bacterial growth was detected with CO_2 production in both bottles. Gram stains from all patients and cultures revealed no micro-organisms. In 14 patients, empiric antibiotic treatment was started (Table 1). The number of patients with signs of peritonitis was unexpectedly high compared with our centre's peritonitis record (one episode/26 months by that time). It was remarkable that peritonitis signs were evident only in patients using bags with lot number M710154 with expiry dates of 2000–9. Patients using imported bags and domestic bags with other lot numbers were symptom free. Additionally, PD fluid in bags with the M710154 lot number appeared darker than usual. After a few days, our suspicion of an aseptic peritonitis induced by one or more chemicals in the PD fluid was strong enough to justify holding antibiotic therapy in all patients. Patients continued PD with bags of another lot number and antibiotics were stopped on 23 October 1996 in 10 patients. In four patients antibiotics were stopped later because of communication problems. In seven patients, antibiotics were never started because of strong evidence for a chemical aetiology (Table 1). The PD bag manufacturer was immediately informed of the problem and fluid samples from lot M710154 were taken. Because of yellow-brownish discoloration of the fluid, which was highly suspicious of increased glucose degradation during heat sterilization, pH and acetaldehyde levels were investigated in the PD fluid with the lot number M710154.

Results

In all patients, dialysate WBC count was above 200 cells/mm^3, with a mean value of 1795 (200–7500) cells/mm^3. All cultures and Gram stains were negative for micro-organisms (Table 1). In all patients, all peritoneal symptoms resolved within 24 h following

Table 1. Clinical and demographic data on 21 chemical peritonitis cases

Patient	Age/ gender	PD since	Perit. date	Cell count	Culture/ G stain	Complaints	Treatment	Treatment dates
1	48/M	30.12.1994	23.10.1996	200	Neg/Neg	CD	–	–
2	35/F	08.07.1996	21.10.1996	600	Neg/Neg	CD	A-S/N*	21–23.10.1996
3	64/M	16.08.1995	23.10.1996	1300	Neg/Neg	CD	–	–
4	46/M	27.10.1995	21.10.1996	800	Neg/Neg	CD, AP	A-S/N*	21–23.10.1996
5	66/M	12.06.1996	18.10.1996	3300	Neg/Neg	CD	A-S/N*	18–23.10.1996
6	53/M	06.06.1995	22.10.1996	3500	Neg/Neg	CD	A-S/N*	22–23.10.1996
7	46/M	11.01.1996	22.10.1996	1400	Neg/Neg	CD, AP	A-S/N*	22–23.10.1996
8	53/M	23.10.1992	21.10.1996	400	Neg/Neg	CD, AP	A-S/N*	21–23.10.1996
9	26/F	12.01.1995	22.10.1996	200	Neg/Neg	CD, AP	–	–
10	47/M	08.04.1996	23.10.1996	9700	Neg/Neg	CD, AP	A-S/N*	23–24.10.1996
11	37/F	27.10.1993	30.10.1996	400	Neg/Neg	CD	–	–
12	63/F	22.12.1994	18.10.1996	1300	Neg/Neg	CD	A-S/N*	18–23.10.1996
13	40/F	28.12.1993	24.10.1996	300	Neg/Neg	CD, AP, Vom	–	–
14	39/F	26.06.1996	25.10.1996	300	–	CD	A-S/N*	25–30.10.1996
15	46/M	12.04.1992	16.10.1996	200	Neg/Neg	CD	–	–
16	48/F	11.07.1995	23.10.1996	300	Neg/Neg	CD, AP	–	–
17	69/F	18.03.1996	15.10.1996	7500	Neg/Neg	CD, AP	A-S/N*	15–23.10.1996
18	57/M	10.06.1996	02.10.1996	1600	Neg/Neg	CD, AP	Ofl/Vanc**	02–23.10.1996
19	39/M	22.07.1996	21.10.1996	1900	Neg/Neg	CD, AP	A-S/N*	21–30.10.1996
20	37/F	25.09.1996	11.11.1996	2200	Neg/Neg	CD, AP	A-S/N*	11–18.11.1996
21	69/M	25.04.1996	16.10.1996	300	Neg/Neg	CD	A-S/N*	16–23.10.1996

*A-S/N, 1000 mg ampicillin + 500 mg sulbactam in each (×4) 2-l bag and netilmicin 40 mg/day as single night-time intraperitoneal dose following 100 mg initial dose; **Ofl/Vanc, ofloxacin 200 mg/day p.o., following 400 mg/day p.o. initial dose, and vancomycin 2000 mg/7 days intraperitoneal dose in one 2-l bag. F, female; M, male; CD, cloudy dialysate; AP, abdominal pain; Neg, negative; G stain, Gram stain; Vom, vomiting.

replacement of the PD bags of lot number M710154 with bags of other lot numbers and with no fluid discoloration. Gas chromatographic analysis in four unused PD solution samples from lot M710154 revealed very high levels of acetaldehyde (17, 17, 19 and 20 p.p.m.), compared with a standard average of 6 p.p.m. in bags that had no brownish discoloration and caused no patient complaints. Acetaldehyde concentrations measured by company analysis in bags with lot number M710154 was also between 17 and 20 p.p.m. In all bags, pH was 5.9.

Based on the above results, and in order to avoid further patient complaints originating from increased glucose degradation products in the fluids, the manufacturer reviewed its heat sterilization process in the production line and reportedly stopped the use of pH 5.9 L-lactate and replaced it with pH 5.3 L-lactate. Following that revision in the heat sterilization process, acetaldehyde concentrations in the bags were below 6 p.p.m., no visible discoloration of the fluid was observed, and no further unusual patient complaints occurred during the use of locally produced PD fluids in Turkey.

Discussion

We have presented 21 patients with mild to moderate symptoms of PD-related peritonitis. Evidence such as negative Gram stain and cultures, sudden, episodic onset in a very large patient population using bags with the same lot number containing a fluid with yellow-brownish discoloration, and immediate disappearence of the symptoms following the replacement of the bags with ones containing clear fluid, strongly suggest an aseptic, dialysis-fluid-related, chemical cause as the aetiological factor in these 21 patients. Chemicals that are known to be potential causes of serositis in PD patients, such as vancomycin [16] or antiseptics [17], were not in use in any of the 21 patients. Furthermore, none of the 21 patients presenting with symptoms of peritonitis were on any intraperitoneal medication before the symptoms appeared. Another potential factor in peritoneal irritation, plasticizers [18], can be ruled out by the fact that symptoms of peritonitis were relieved by stopping the use of bags from lot M710154 and continuing dialysis with bags with different lot numbers yet containing the same plastic material. Another potential cause of peritoneal irritation, glucose degradation products [19], may be the most likely explanation for the cases of aseptic serositis presented here. The yellow-brown, darker appearance of the fluid is typical of 'caramelized' sugar in the fluids. We should have investigated other glucose degradation products in the bags with lot number 710154, but we had no way of preserving the bags; levels of glucose degradation products would have increased over time, and the procedure might have given rise to misleading results. We decided to investigate dialysate acetaldehyde concentrations immediately. Very high acetaldehyde levels in the suspected batch and relief of symptoms following the use of bags known to have lower acetaldehyde content are very suggestive of an acetaldehyde-induced chemical peritonitis epidemic in the cases presented above. Following feedback from our hospital, procedural changes were made in the newly established production line and no similar problems have occurred since.

Although it is not clear which particular glucose degradation product is responsible for their cytotoxic effects [12], it is well known that glucose degradation products in commercially available PD solutions may contribute to peritoneal membrane injury as evidenced by their *in vitro* effects such as impairing mouse fibroblast cellular growth and altering inflammatory response [20]. There is only limited clinical evidence to prove that any glucose degradation product has induced PD fluid side-effects in human beings, including reversible loss of ultrafiltration and abdominal pain induced by PD bags towards the end of their shelf life [14,15]. The findings and observations given above may be the first clinical evidence that acetaldehyde and possibly other glucose degradation products, in concentrations 3–4 times higher than usual in commercial PD bags, may induce acute, chemical peritonitis. If so, the long-term effects of glucose degradation products in commercial PD solutions should be cautiously investigated.

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