SHORT REPORTS

Epidemic of Chemical Peritonitis in Patients on Continuous Ambulatory Peritoneal Dialysis: A Report from Western India

While non-infectious etiologies like chemical irritants are rare causes of epidemics of peritonitis, this possibility should be considered when one encounters an unusual clustering of peritonitis cases. We describe here an epidemic of chemical peritonitis at our center.

Perit Dial Int 2016; 36(3):347–349

www.PDConnect.com

<http://dx.doi.org/10.3747/pdi.2015.00055>

KEY WORDS: Sterile peritonitis; glucose degradation products; epidemic.

Advances in technique have drastically decreased the peritonitis rate to as low as 1 in 48 – 56 patient months (1). Non-infectious etiologies like chemical irritants are rare but important causes of epidemics of peritonitis (2,3). This possibility should always be kept in mind when one encounters an unusual clustering of peritonitis cases. We describe here an epidemic of chemical peritonitis at our center.

MATERIAL AND METHODS

From 15 April 2014 to 5 June 2014, 13 patients on continuous ambulatory peritoneal dialysis (CAPD) developed peritonitis. Detailed history focussing on breach in technique, visual appearance of fluid before and after exchange, presence of abdominal pain, fever, chills, vomiting, diarrhea, ultrafiltration failure, and exit-site care was recorded. Physical examination focussing on vital signs, evidence of hypervolemia, appearance of the exit site, effluent, abdominal tenderness, guarding, and rigidity was done at the hospital.

Effluent was studied for gram stain and culture (direct inoculation after centrifugation of 50 mL of fluid or direct inoculation in blood culture broth if received in off-office hours). In view of culture negativity, effluent was further studied by subcultures, repeat inoculation, fungal culture, culture for fastidious organisms, and endotoxin levels. Due to clustering of cases within a short period of time and use of a common dialysate batch from a newly started manufacturing facility, a detailed chemical analysis was undertaken. Osmolality, pH, high pressure liquid chromatography (HPLC), and mass spectroscopy analysis for constituents of dialysate were done on the suspect and control batches (fluid manufactured at previous facility).

Dialysate was tested for presence of acetaldehyde by HPLC (Jasco, MD, USA) using a Spherisorb S5P column (Waters, MA, USA). Separation of acetaldehyde was performed using ammonium acetate (11.6 g/L, pH 4.0) as mobile phase with a flow rate of 0.45 mL/min and 25°C column temperature. Detection was carried out using a UV/VIS detector at 284 nm. All reagents used for this analysis were of HPLC grade. Standards of acetaldehyde were diluted to 36 ppm in the mobile phase. Similarly, dialysis fluids were diluted 5-fold in the mobile phase solvent. For liquid chromatography mass spectrometry (LC-MS) analysis, 1 mL of the dialysate from each bag was extracted with the same volume of diethyl ether. Extracted samples were dried overnight at 25°C and resuspended in the mobile phase for LC-MS analysis. Samples were filtered through a 0.22-μm filter before analysis. The LC-MS analysis of components was done using an Agilent MS Q-TOF G6550A system using a C18 column (HiQ Sil C18W; Kya Tech corporation, Tokyo, Japan). The mobile phase used for separation was water:acetonitrile:trifluoroacetic acid (TFA) (700:300:1) at a flow rate of 0.4 mL/min. The column temperature was maintained at 25°C. Mass spectrometric analysis was carried out using the positive electrospray ionisation technique.

RESULTS

From 15 April 2014 to 5 June 2014, 13 of 26 patients on peritoneal dialysis (PD) were evaluated for peritonitis. Median age of patients was 56 years (range from 15 to 74 years), and 6 were males (46.5%). All 13 (100%) had cloudy effluent, 11/13 (76.47%) had abdominal pain, and 5/13 (38.4%) had systemic symptoms in the form of fever and chills. Ultrafiltration failure was noted in 5/13 (38.4%) patients.

Five of 13 patients reported altered darker appearance of the dialysate before exchange. All the patients were using a common batch of 1.5% dextrose for exchanges. Median effluent cell count was 2,000 cells/mm³ (range: 260 – 10,000 cells/mm³) with 85% polymorphs, eosinophils were absent, and gram stain and culture were negative in 11/13 patients. All 13 had negative fungal cultures. Two patients' effluent grew *Staphylococcus aureus*.

The endotoxin level tested on the common suspect batch was < 0.25 EU/mL. Acetaldehyde was not detectable in the samples tested by HPLC analysis. Further, LC-MS analysis was done to identify the difference in terms of chemical entities between 2 batches of dialysate. The chromatograms obtained indicated the presence of several extra peaks in samples corresponding to suspect dialysate, suggesting the existence of additional chemical entities (Figure 1).

Figure 1 — High pressure liquid chromatography analysis of suspect (top) and control (bottom) batches of fluid. At absorption maxima of 284 nm, fluid A shows 5 peaks while fluid B shows 3 peaks, indicating the presence of additional entities in the suspect batch of peritoneal dialysis fluid.

Mass spectrometric analysis showed that these peaks primarily contained compounds of molecular weight (MW 90) and 118 (Figure 2). These compounds likely are glucose degradation products (GDPs); the MWs observed are similar to those of degradation products reported on heat treatment of glucose (4) (glyceraldehyde dimer and erythrose both have MW 120, glyceraldehyde has a MW 90). In addition, several higher MW compounds (MW 299, 305, 335, 395) were also present. These presumably have been formed by polymerization of glucose itself, or of its degradation products.

DISCUSSION

We encountered an epidemic of peritonitis that turned out to be due to several low MW compounds with characteristics similar to glucose degradation products. In addition, high MW compounds arising from polymerization may have played a role in this epidemic. Clustering of cases within 2 months, culture negativity in the majority, visible change in the appearance of a suspect common batch manufactured at a newly started

Figure 2 — Liquid chromatography mass spectrometry analysis of normal (top) and suspect (bottom) dialysate batches. Extra peaks with considerable concentration difference are circled. Each peak was further analyzed for major compounds present based on different masses present (based on m/z ratio). Data is not shown for different masses present.

facility, and, finally, detailed chemical evaluation confirmed the etiology of this epidemic.

Chemical peritonitis is a rare but important cause of sterile peritonitis. Higher pH and longer sterilisation time can lead to the formation of several known and unidentifiable glucose degradation products like formaldehyde, acetaldehyde, 5-hydroxymethyl-2-furfural, glyoxal, 2-furaldehyde, methylglyoxal, and some still unidentified biologically active compounds (5). Tuncer *et al.* studied 21 cases of sterile peritonitis in Turkey and noted acetaldehyde as the culprit GDP whose concentration was found to be 17 – 20 ppm (3). In a report from Iran, Nouri-Majalan *et al.* reported 20 cases of sterile peritonitis (6). Malfunction of the autoclave leading to excessive heating and consequent generation of GDPs was thought to be the cause. However, in both these reports, studies for endotoxins and detailed further investigations were not performed.

We ruled out bacterial contamination in 11/13 cases by repeated cultures, subculture, and cultures for fastidious organisms and fungi. Visible change in the appearance of fluid, clustering of cases, culture negativity, recent change in the manufacturing facility, and association with a common dialysate batch of 1.5% dextrose all led us to suspect the possibility of contamination at source. Endotoxin studies performed from a Food and Drug Administration (FDA)-approved lab showed negative results.

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Unlike in a previous report (5), acetaldehyde was not responsible for the current epidemic of peritonitis. The LC-MS analysis of additional peaks observed in the suspect batch suggested similarity to reported GDPs. Formation of similar compounds on heat treatment of glucose was reported (7). Several higher MW compounds (MW 299, 305, 335, 395) were also present. These were presumably formed by polymerization of glucose itself, or of its degradation products, consistent with previous reports on glucose polymerization on heat treatment (4). These GDPs are highly reactive, and form higher MW compounds as the reaction time increases. The extent of glucose polymerization is also dependent on the rate of heating; with slow heating rates favoring re-polymerization. This indicates that changes in autoclaving conditions of dialysate might have led to the formation of glucose polymerization products. The compound libraries available with us were not exhaustive enough to definitively identify the higher MW compounds. It is further possible that the fluid may have contained some additional compounds which were not extracted in diethyl ether during sample preparation.

The LC-MS analysis showed that it was very likely that both GDPs and polymerization products were present in the suspect batch of dialysate and had a role in this epidemic of chemical peritonitis. Like previous studies, this study gives more insight into the involvement of GDPs (other than acetaldehyde), as well as several high MW entities, in chemical peritonitis. It is clear from this study that systematic use of analytical techniques such as HPLC and LC-MS has the potential to give a quick and detailed understanding of chemical entities involved in peritonitis. This is the first study reporting the advanced techniques for probing chemical peritonitis. Further analysis using standards of expected chemical entities using MS and LC-MS is required for detailed probing of molecular entities involved in current epidemics of peritonitis.

Unless suspected and diagnosed in time, chemical peritonitis can be associated with significant morbidity. Four of our patients had their catheter removed after being declared resistant to treatment. This, of course, occurred before we suspected a point source and a common culprit batch. Such episodes can be a serious threat to the credibility and acceptance (both by patients and doctors) of PD. Utmost care should be taken by manufacturers to prevent such accidents.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

Tukaram Jamale^{1*}
Aniruddha Dhokare¹
Kushal Satpute²
Renu Kulkarni²
Deepa Usulumarty³
Billa Vishwanath³
Santosh Noronha²
Niwrutti Hase¹

Nephrology¹

Seth GS Medical college, KEM Hospital, Mumbai, India

Chemical Engineering²
Indian Institute of Technology, Mumbai, India
Nephrology³
Bombay Hospital Institute of Medical Sciences
Mumbai, India

*email: tukaramjamale@yahoo.co.in

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