A new, safe and convenient 5-L dual-chamber container for automated peritoneal dialysis

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Abstract

Background. Automated peritoneal dialysis (APD) provides the opportunity for home-based dialysis, enabling the patient to optimize their lifestyle by maintaining their normal daily routine. Use of a larger bag size and biocompatible solution is desirable. In an effort to further improve patient convenience and reduce the probability of infusing only the buffer contents from the outflow chamber, we designed a 5-L dual-chamber container system with a dual-seal system consisting of a long seal between the dextrose chamber and buffer chambers and a short SafetyMoon™ seal between the buffer chamber and container outflow connector.

Methods. The safety and effectiveness of this new container system was assessed in a non-interventional, prospective, open-label, multi-centre, uncontrolled, Baxter-sponsored post-authorization safety study in 249 patients from 7 countries in Europe.

Results. No mis-infusion events were noted throughout the study where 68 519 Physioneal™ 5-L bags in ClearFlex™ were used for an average (SD) of 4.3 (1.9) months per patient. Overall, the percentage of patients and/or care providers rating the 5-L bag preparation as very easy or easy at baseline (0–8 weeks), 9–16, 17–24 and 25–32 weeks ranged from 94 to 97%. Assuming a Poisson distribution for the bag count data, the estimated change in number of bicarbonate/lactate dialysis fluid bags (5 or 2.5 L) as a percent of prior bag use was −36%, while the estimated change in number of bags for ALL solutions as a percent of prior bag use was −31%. The predominant reasons given by the investigators for prescribing 5-L PD solutions at study onset were biocompatibility, easier and convenient for their patients to use, physiological pH and less bag connections. None of the 92 serious adverse events were suspected to be related to the Physioneal 5-L PD solution.

Conclusions. Use of a larger, Physioneal 5-L bag mitigates the concern regarding the possibility of mis-infusing the buffer chamber solution, is convenient to use by the patient/health care provider and is associated with more than a 30% reduction in the weekly number of dialysis solution bags required per patient for their APD therapy.

Keywords: automated peritoneal dialysis (APD); biocompatibility mis-infusion; Physioneal; solutions

Introduction

Automated peritoneal dialysis (APD) provides the opportunity for home-based dialysis, enabling the patient to optimize their lifestyle by maintaining their normal daily routine. Use of a more appropriate bag size is important in improving the convenience of this home-based therapy since larger bag volumes would require fewer bag connections. Furthermore, use of biocompatible solutions has become more desirable in recent years due to in vitro and animal studies suggesting that these solutions are associated with less impairment of host defences and peritoneal membrane function compared to conventional glucose-containing lactate-buffered solutions [1–11].

Physioneal™ is a glucose-based peritoneal dialysis solution with a physiologic bicarbonate/lactate buffer, presented in a dual-chamber container which separates the glucose-containing solution from the alkaline bicarbonate/lactate or buffer solution, allowing bicarbonate to be separated from calcium and magnesium in order to prevent precipitation of calcium carbonate during sterilization and storage [1–3]. It has been shown to be safe and effective in patients on CAPD and APD, and its use is associated with reduced infusion pain [12–14].

One need has been in designing a bicarbonate/lactate 5-L dual-chamber bag for APD to maximize patient convenience. Inherent in this bag’s design is the need to minimize the risk of infusing the un-mixed content of the buffer chamber that is adjacent to the bag outflow tract to the pa-
tient’s peritoneal cavity. Infusion of un-mixed solution from the buffer chamber may be associated with abdominal discomfort or pain and disturbances in fluid and electrolytes or acid–base balance.

In an effort to further improve patient safety and reduce the probability of infusing only the buffer content from the outflow chamber, which could occur with improper preparation of the container content, we designed a 5-L dual-chamber container system (characterized in Figure 1) with a dual-seal system consisting of a long seal between the dextrose chamber (pH 2.0) and buffer chamber (pH 9.0) with a short SafetyMoon™ seal between the buffer chamber and container outflow connector. This dual-seal system is designed to minimize the risk of mis-infusion (MI) by making the long seal easier to open than the shorter safety seal.

We hypothesized that the larger-sized container would be more convenient for the APD patient and homecare provider by reducing the number of connections required for preparing a 24-h APD therapy. This report summarizes the effectiveness of this 5-L, dual-chamber, dual-seal container system in preventing MI of the buffer chamber contents of this PD solution and assesses its impact on patient convenience during APD therapy.

Materials and methods

Study design and population

This was a non-interventional, prospective, open-label, multi-centre, uncontrolled, Baxter-sponsored post-authorization safety study (PASS) of bicarbonate/lactate-based PD solutions containing either 35 or 40 meq/L of buffer in a in a 5-L, dual-chamber, dual-seal container in patients treated by APD age 18 years or older. The design and scope of the PASS, defined as

"a pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of marketing authorizations, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product", was conducted in compliance with the European Guidance on Post Authorisation Safety Studies as defined in EudraLex Vol 9A [15]. The medicinal product was prescribed in the usual manner in accordance with the terms of the marketing authorization. No additional diagnostic or monitoring procedures were required. Duration of the PASS participation varied between a minimum of 2 weeks and up to ~7 months. Experienced sites with high-volume usage of bicarbonate/lactate-buffered PD solutions were selected for participation in the study.

All clinical data were collected during the routine patient–nurse or physician contacts and included the following: MI data, product ease of use data, product quality complaints, demographics, PD therapy prescription information and safety data.

A MI was defined as an infusion of un-mixed solution (small chamber or concentrate buffer solution) into the peritoneal cavity with or without clinical symptoms. If a MI occurred, it was reported during the routine patient–nurse or physician contacts or during spontaneous calls.

The following questions assessed the performance of the 5-L container and focussed on capturing MIs:

* Did any of the seals fail to open properly since the last contact?
* At any time, did you infuse un-mixed solution from only the small chamber?

Ease of use was assessed by asking the patient/care provider to rate [very easy (VE), easy (E), difficult (D) or very difficult (VD)] their ability to open the overpouch, long seal and short seal and connect the bags to the HomeChoice cycler. They were also asked to rate their overall ease of preparing and using the 5-L dialysis bags.

The study was designed to accept a MI rate of 0.01%. Therefore, the upper bound of a 95% confidence interval equal to 0.01% required that a minimum of 60 000 dual-chambered bags be studied. Given an expected dropout rate of 12.5% over a 3-month period and an expected bag usage number of two to three bags per night therapy, a minimum of 245 patients were needed for enrolment in order to reach our bag usage goal within a 6- to 9-month period.

The decision to stop the study and conduct a full analysis of the data was done after at least 60 000 dialysis 5-L bags had been prepared and

![Fig. 1. Preparation steps of the Physioneal 5-L bag.](https://academic.oup.com/ndt/article/26/1/299/1833607)
Overall, how easy or difficult is it for you to your previous product? 

Questions

<table>
<thead>
<tr>
<th>Questions</th>
<th>% of patients rating ease of use question as ‘very easy’ or ‘easy’ at varying time points</th>
</tr>
</thead>
<tbody>
<tr>
<td>How easy or difficult is it for you to open the overpouch?</td>
<td>0-8 weeks  9-16 weeks  17-24 weeks  25-32 weeks</td>
</tr>
<tr>
<td>How easy or difficult is it for you to open the long seal?</td>
<td>97.9 (186/190)  100 (145/145)  99.2 (121/122)  98.3 (58/59)</td>
</tr>
<tr>
<td>How easy or difficult is it for you to open the short seal?</td>
<td>82.1 (156/190)  91 (132/145)  92.6 (113/122)  86.4 (51/59)</td>
</tr>
<tr>
<td>How easy or difficult is it for you to prepare the bags?</td>
<td>84.2 (160/190)  89.7 (130/145)  94.3 (115/122)  86.4 (51/59)</td>
</tr>
<tr>
<td>Overall, how easy or difficult is it for you to prepare the bags?</td>
<td>93.7 (178/190)  96.6 (140/145)  95.9 (117/122)  96.6 (57/59)</td>
</tr>
<tr>
<td>Overall, how easy or difficult is it for you to use the Physioneal 5-L bag (compared to your previous product)?</td>
<td>92.1 (152/165)  98.6 (68/69)  94.3 (66/70)  96.6 (56/58)</td>
</tr>
</tbody>
</table>

Statistical analysis

The frequency and corresponding percentages of responses to each of the product use questions was determined. The total number of bag infusions used in a minimum of 200 patients. All patients were required to be enrolled for at least 2 weeks.

Study product

The 5-L container is a dual-chambered, dual-seal, PD solution container. The safety of administration is ensured by the sequential opening of the seals according to the recommended protocol described in Figure 1. If the second or short SafetyMoon™ seal is not activated, no PD solution will be infused into the peritoneal cavity. However, activation of the short SafetyMoon™ seal only without activation of the long seal, which enables mixing of the dextrose chamber with the buffer chamber, could potentially lead to a MI of the buffer chamber solution. The products used in this study were bicarbonate/lactate-based buffer PD solutions containing either 35 or 40 meq/L of buffer in a 5-L container with glucose 1.36, 2.27 and 3.86%. The PD solutions were administered intraperitoneally using a peritoneal dialysis cycler and were intended for use in an APD setting, in combination with the HomeChoice/PRO devices.

Results

Demographics

A total of 249 patients using 5-L bicarbonate/lactate PD solutions in an APD treatment setting were enrolled in the study. The baseline characteristics of these patients are summarized in Table 1. Twenty-nine (11.6%) of the 249 patients discontinued the study before completing the planned study duration. The patient population was primarily male and Caucasian. The mean duration of chronic dialysis therapy was 2.7 years (range=4 days–35 years), while the mean duration of the current APD therapy regimen was 1.8 years.

Mis-infusion and seal assessment

A total of 68 519 Physioneal 5-L bags were prepared during the study. No MIs or potential MIs were reported during the study. None of the 249 enrolled patients replied affirmative to either of the above questions during the time they were on the study. Questionnaire results indicated that the seals were activated in the proper sequence.

Ease of use

The ease of use results for the 5-L dialysis container are summarized in Table 2. Most patients with a baseline rating was calculated from first infusion to last infusion of the PD solution, taking into account prescriptions, prescription changes and treatment interruptions. The average weekly number of bags used (infusions) per subject was calculated and summarized. The change in the average weekly number of bags used per subject (increase or decrease) between prior to the study (baseline prescription) and during the study was calculated and summarized. In addition, a 95% confidence interval for the estimated change in number of bags used as a percent of prior bag use (baseline prescription) was calculated assuming a Poisson distribution for the bag count data. The SAS procedure named GENMOD was used.

The time at risk for peritonitis (extent of exposure) was defined as the total number of study days from first infusion to last infusion of the 5-L dialysis bag. The adjusted rate of peritonitis was determined by dividing the number of peritonitis episodes over the study by patient-months (number of patients multiplied by the study duration per patient) and expressed as one episode per X patient-months. The 95% confidence limits for the rates of peritonitis were also determined. In addition, time between events was summarized. Using the product-limit method of the SAS procedure, LIFETEST, the 95% confidence limits for the estimated probability of ‘survival’ defined by remaining peritonitis-free after X days following the first dose was determined.
of difficult (D) or very difficult (VD) demonstrated E or VE rating at follow-up. Compared to patient and/or care provider’s experience before 5-L dialysis availability, the percentage of patients and/or care providers rating the 5-L dialysis bag as much easier or easier at the time points ranged from 92 to 99% (see Table 2).

**Therapy data**

The average weekly number of bags used per patient before and during the study is presented in Table 3 as a routine summary statistic. For statistical analysis purposes, we gave additional consideration to the underlying theoretical distribution for count data since the bag count data would be expected to follow a Poisson distribution instead of a normal distribution. As further evidence of non-normality in the distribution of change in bag count, skewness is noted where the means are consistently higher than the medians due to the occurrence of extreme values (i.e. large increases). Assuming a Poisson distribution for the bag count data, the estimated change in number of Physioneal 2.5 L bags as a percent of prior bag use was −36% (i.e. a decrease) with 95% confidence interval for this estimate from −39 to −33%. Similarly, the estimated change in number of bags for ALL solutions as a percent of prior bag use was −31%, (i.e. a decrease), with a 95% confidence interval for this estimate from −29 to −34%.

The predominant reasons given by the investigators for prescribing the 5-L PD solution container at study onset were biocompatibility (70.3%, 175 of 249), easier to use (56.6%, 141 of 249), physiological pH (56.2%, 140 of 249) and less bag connections.

**Safety data**

One hundred twenty-eight AEs were reported in 77 (30.9%) of the 249 enrolled patients. Thirty (30) patients had at least one peritonitis event during the study corresponding to a peritonitis rate of 1 episode per 27.3 patient-months. None of the 30 patients had peritonitis events that were attributed to the treatment by the investigators or by Baxter. Twenty-seven bacterial peritonitis events were reported in 26 (10.4%) of the patients, 6 peritonitis events (presumed to represent culture-negative bacterial peritonitis since patients improved with antibiotic treatment) were reported in 5 (2.0%) of the patients and 1 fungal peritonitis event was reported in 1 (0.4%) patient.

A patient’s prescription may include more than one solution.

**Discussion**

This PASS study was designed to assess the safety and ease of use of a dual-chamber, dual-seal 5-L container for a bicarbonate/lactate-buffered PD solution (Physioneal™). The results of this study demonstrate that this 5-L, dual-seal container mitigates the risk of MI since no MIs occurred during the study period where more than 68,000 bags were used for APD therapies.

Two of the primary reasons for prescribing the 5-L PD solution were that the 5-L container system was expected to be easier and more convenient to use and required fewer bag connections compared to the same product in a 2.5-L container. In fact, study data supported these expectations since a large majority of patients found the 5-L container ‘very easy’ or ‘easy’ to use with respect to opening the overpouch, opening the long and the short seals, connecting the container to the HomeChoice lines and overall preparation of the 5-L bags throughout the study. On average, use of the 5-L solution was associated with more than a 30% reduction in the weekly number of PD solution bags and overall number of all dialysis solution bags required per subject for APD compared to the APD regimen prior to availability of the 5-L container. Taken together, these results support our original hypothesis that use of the 5-L container provides a more convenient means of providing APD therapy for patients. This is an important finding of this study since the physical aspects of connecting multiple dialysis solution bags using sterile technique is a well-known burden of PD to patients and their home care partners [16].

None of the AEs or withdrawals due to AEs was considered to be related to the 5-L solution. Furthermore, the peritonitis rate of 1 episode per 27.3 patient-months noted in this study did not differ from the peritonitis rate of 1 in 25.1 patient-months reported in two single-centre reports in Western Europe [17,18].

**Conclusion**

In conclusion, the 5-L, non-PVC, dual-chamber, dual-seal container system for this bicarbonate/lactate-buffered PD solution (Physioneal™) mitigates the concern regarding the possibility of mis-infusing the buffer chamber solution. Furthermore, use of a larger container system was shown to be convenient to use by the patient/health care provider and was associated with more than a 30% reduction in the weekly number of dialysis solution bags required per patient for their APD therapy.

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**Table 3. Average weekly number of bags per patient**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bag count/patient (pre-study)</th>
<th>Bag count/patient (during study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Physioneal 2.5 L</td>
<td>167</td>
<td>30.1 (12.5)</td>
</tr>
<tr>
<td>Physioneal 5 L CF</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Physioneal 2.5 L</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>or 5 L CF</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>All solutions</td>
<td>223</td>
<td>33.7 (12.0)</td>
</tr>
</tbody>
</table>
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