Original Article

Hypertonic glucose-based peritoneal dialysate is associated with higher blood pressure and adverse haemodynamics as compared with icodextrin

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Abstract

Background. Little is known about the haemodynamic effects of continuous ambulatory peritoneal dialysis (CAPD) despite its widespread use in the management of end-stage renal failure. We undertook a study to delineate the haemodynamic effects of CAPD using glucose-containing fluids (1.36 and 3.86% glucose) and icodextrin.

Methods. Eight CAPD patients were recruited for a prospective crossover study. Patients attended for two investigatory days (in random order). CAPD was carried out using 1.36% followed by 3.86% glucose (buffered with lactate/bicarbonate, Physioneal®) on one study day and 1.36% glucose followed by 7.5% icodextrin (Extraneal®) on the other day. Dwell times were 150 min. Blood pressure (BP) and a full range of haemodynamic variables including pulse (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were measured non-invasively using continuous arterial pulse wave analysis.

Results. BP was significantly higher during 3.86% glucose dwells as compared with 1.36% glucose or icodextrin dwells (P < 0.0001). TPR during all three dwells was similar; the higher blood pressure was due to an increased HR, SV and, therefore, CO during 3.86% glucose dwells. The higher blood pressure during the 3.86% glucose dwells was present despite the highest ultrafiltration volume and sodium removal.

Conclusion. This study demonstrates large magnitude haemodynamic changes in response to CAPD. In addition to the well-recognized adverse effects on blood glucose and long-term peritoneal membrane viability, CAPD fluids containing high glucose concentrations may also exert undesirable effects on systemic haemodynamics, with potential long-term consequences for patient outcomes.

Keywords: glucose-based dialysate; haemodynamics; icodextrin; peritoneal dialysis; pulse wave analysis

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) is a well-established therapy that is used to treat 15–50% of dialysis patients [1]. However, little is known about the haemodynamic response to CAPD. One recent study suggested significant haemodynamic changes during a 30 min dwell of a standard peritoneal permeability analysis [2], but other work on this subject dating back >20 years used intermittent monitoring techniques and produced conflicting data.

It is becoming increasingly recognized that glucose has limitations as the osmotic agent in peritoneal dialysate. Glucose and glucose degradation products (GDPs) are toxic to the peritoneum [3], and glucose is also systemically absorbed, leading to hyperinsulinaemia plus weight gain [4]. This has driven the development of other dialysate solutions, including icodextrin (Extraneal®). Icodextrin reduces systemic glucose absorption and achieves equivalent ultrafiltration as compared with hypertonic glucose fluids during prolonged intraperitoneal dwells [5].

Currently there are no data available on the haemodynamic effects directly attributable to glucose-containing or alternative dialysate fluids. Therefore, we undertook this study to examine the hypotheses that CAPD is associated with significant haemodynamic change, and that 1.36% glucose, 3.86% glucose and icodextrin containing-dialysate fluids exert differing haemodynamic effects.
Subjects and methods

Patients

We recruited eight patients on CAPD for a prospective cross-over study. Baseline characteristics and CAPD prescriptions are shown in Table 1. All patients had been on CAPD for >6 months (mean 40.5 months, range 18–73). All had a weekly Kt/V of >2.0 of which <50% was provided by residual renal function. One patient was anuric.

Patients were eligible only if their blood pressure had been stable (BP <140/85 mmHg with no changes in anti-hypertensive medications) over the 4 weeks prior to recruitment, and if <50% of their PD regime was made up of 3.86% glucose solution or icodextrin. Patients were excluded if they had severe peripheral vascular disease, or if they had an arterio-venous fistula or renal transplant in situ.

All patients underwent clinical examination prior to commencing the study to ensure that they were at their optimal weight. All patients underwent standard peritoneal equilibration testing (PET) and assessment of dialysis adequacy (Adequest 2.0®, Baxter Healthcare, Norfolk, UK).

Study protocol

All patients gave informed consent prior to commencement, and ethical approval for the project was granted by Derbyshire Local Research Ethics Committee. Patients were asked to attend for two study days (A and B), the order of which was randomly determined. For each investigatory session, patients were admitted to a clinical investigations unit where CAPD was performed. All fluids were manufactured by Baxter Healthcare (Norfolk, UK) and were warmed to 37°C before instillation. Non-invasive haemodynamic monitoring was undertaken using a Finometer, which was fitted for the entirety of each session. To obtain baseline values, monitoring commenced 30 min prior to draining the night-time dwell. On day A, patients underwent CAPD with 2.5 l of low osmolar Physioneal® (bicarbonate/lactate-based pH neutral fluid containing 1.36% glucose) followed by high osmolar Physioneal® (3.86% glucose). Dwell times were 150 min and each drain/dwell cycle was planned to last ~3 h, although this was not absolute due to variable draining times of different patients. On day B, 2.5 l of icodextrin was substituted for the 3.86% Physioneal® but the protocol was otherwise identical. There was at least a week’s washout period between the two study days. Patients were allowed a light breakfast 2 h before the first CAPD exchange, and were supplied with a standardized midday meal that was consumed 1 h before the second CAPD exchange. Blood samples were collected before and after each session in lithium heparin and EDTA tubes, and biochemical analysis was performed on a multichannel autoanalyser. The volume and electrolyte concentration of the peritoneal waste fluid were also assessed. Primary end-points were percentage change in BP, stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) in response to different PD dialysate fluids.

Finometer

The Finometer (Finapres Medical Systems, Arnhem, The Netherlands) allows continuous non-invasive pulse wave analysis at the digital artery [6]. The technology utilizes the finger-clamp method to record digital artery pulse waveform, and from this reconstructs a central aortic waveform that allows calculation of a full range of haemodynamic variables on a continuous basis, for each heart beat [7]. These include pulse rate (HR), BP, SV, CO and TPR. This technology is becoming increasingly used to assess chronic dialysis patients [2,8,9]. Previous work has validated the Finometer against invasive haemodynamic measurements in normals, unstable intensive care patients and in cardiac surgery patients, a proportion of whom had vascular calcification [10–12]. This has shown the Finometer to be accurate in tracking relative change. Data are therefore presented as percentage change from baseline, except for BP, which is
calibrated against brachial readings using a return to flow method, and for this absolute values are shown.

**Statistical analysis**

Results are expressed as mean±SD. For BP and haemodynamic data, the mean refers to the complete dwell period, and these data were compared using one-way analysis of variance (ANOVA) with a design for repeated measures and Bonferroni’s test to correct for multiple comparisons. For other data, the paired t-test was used after significant deviations from a normal distribution were excluded with the Kolmogorov–Smirnov test. Correlation coefficients were calculated using Pearson’s test. An alpha error at $P < 0.05$ was judged to be significant.

**Results**

**Blood pressure and heart rate during dwell periods**

We found BP to be significantly higher during 3.86% glucose dwells as compared with both 1.36% glucose and icodextrin dwells ($P < 0.0001$). The mean systolic BP (SBP) for the entire dwell with 1.36% glucose was $149.8 ± 4.4$ mmHg, the mean diastolic BP (DBP) was $86.6 ± 3.4$ mmHg and the mean of the mean arterial pressure (MAP) was $109.5 ± 3.9$ mmHg. During the 3.86% glucose dwell, all three BP parameters were higher; the mean SBP for the entire dwell was $159.9 ± 6.3$ mmHg ($P < 0.001$), mean DBP was $93.9 ± 4.3$ mmHg ($P < 0.001$) and mean MAP was $117.5 ± 5.1$ mmHg ($P < 0.001$). During the icodextrin dwell, the mean SBP for the entire dwell was $159.9 ± 6.3$ mmHg ($P < 0.001$), mean DBP was $93.9 ± 4.3$ mmHg ($P < 0.001$) and mean MAP was $117.5 ± 5.1$ mmHg ($P < 0.001$). During the 3.86% glucose dwell, the mean SBP for the entire dwell was $159.9 ± 6.3$ mmHg ($P < 0.001$), mean DBP was $93.9 ± 4.3$ mmHg ($P < 0.001$) and mean MAP was $117.5 ± 5.1$ mmHg ($P < 0.001$). During the icodextrin dwell, the mean SBP for the entire dwell was $159.9 ± 6.3$ mmHg ($P < 0.001$), mean DBP was $93.9 ± 4.3$ mmHg ($P < 0.001$) and mean MAP was $117.5 ± 5.1$ mmHg ($P < 0.001$). Comparing mean BP during 3.86% glucose dwells with icodextrin dwells, readings were significantly higher during the former for SBP, DBP and MAP ($P < 0.001$ for each). BP data are summarized in Figure 1.

We also found significant differences in HR between 3.86% glucose dwells and both the 1.36% glucose and icodextrin dwells ($P = 0.0004$). Mean HR for the entire 1.36% glucose and icodextrin dwell periods were not significantly different at $–4.3 ± 1.99$ and $–4.17 ± 1.41$%, respectively ($P = 0.74$). The mean HR during the 3.86% glucose dwell was $–2.27 ± 2.94$% and this was significantly greater than either the 1.36% glucose ($P = 0.002$) or the icodextrin dwell periods ($P = 0.002$). These data are summarized in Figure 2.

**Haemodynamic data during dwell periods**

SV and CO were also found to be significantly higher during the 3.86% glucose dwells ($P < 0.0001$). During the 1.36% glucose dwell, mean SV for the whole period was $–5.69 ± 6.30$%. After an initial increase, SV during the icodextrin dwell was stable, with a mean for the entire period of $–8.05 ± 3.92$%, which was not statistically different from the 1.36% glucose dwell ($P = 0.08$). During the 3.86% glucose dwell, the mean SV for the entire period was $–1.18 ± 7.52$%, which was significantly higher than both the 1.36% glucose ($P < 0.001$) and icodextrin dwell periods ($P < 0.001$).

As the product of SV and HR, CO showed similar changes. Mean CO for the whole dwell period with 1.36% glucose was $–10.47 ± 6.86$%. CO increased initially for both icodextrin and 3.86% glucose fluids, but to a much greater extent with 3.86% glucose. For the icodextrin dwell, the mean for the entire period was $–12.6 ± 3.90$$. The mean CO for the 3.86% glucose dwell was $–4.21 ± 8.44$%, which was significantly higher than the 1.36% glucose ($P < 0.001$) and icodextrin dwells ($P < 0.001$).
TPR increased progressively during all three dwell phases at a similar rate and by a similar magnitude. Mean TPR for the entire dwell period was $+25.79 \pm 13.09\%$ for 1.36% glucose, $+30.64 \pm 16.07\%$ for 3.86% glucose and $+28.15 \pm 11.02\%$ for icodextrin. There were no significant differences between these mean values ($P = 0.092$). All haemodynamic data are summarized in Figure 2.

The haemodynamic and BP patterns described above are population means. Analysing patients individually, seven out of eight exhibited similar patterns for BP. Two of the three diabetic patients were insulin treated and they did not display a higher SV and CO during the 3.86% glucose dwell, as compared with the non-insulin-treated patient who did behave in a similar overall fashion. No insulin was administered during the study periods.

**Haemodynamic data during drain/fill periods**

Individual responses during drainage and instillation of dialysate fluid were heterogeneous, and in some individuals were of large magnitude. However, there were no significant differences in BP or any of the haemodynamic variables when comparing the different dialysate fluids during drain/fill phases.

**Ultrafiltration volumes and sodium removal**

The mean ultrafiltration (UF) volume during the 3.86% glucose dwell was $500 \pm 290\text{ ml}$. This value was significantly higher than both the icodextrin dwell with a mean of $243.8 \pm 111\text{ ml}$ ($P = 0.028$) and the 1.36% glucose dwell with a mean of $143.8 \pm 96.3\text{ ml}$ ($P = 0.001$). The difference between the mean UF volumes with icodextrin vs 1.36% glucose was of borderline statistical significance ($P = 0.057$). There was no correlation between BP and UF volume. These data are summarized in Figure 3.

There were no significant differences in sodium loss between icodextrin and 3.86% glucose dwells...
response to the cooling effect of instilling dialysate. Haemodialysis patients experiencing progressive UF demonstrate a rise in TPR in association with an increase in peripheral sympathetic nerve activity [17], and an alternative explanation would be that the UF of PD causes a compensatory rise in TPR in response to volume contraction [18].

The observed changes in haemodynamic parameters were apparent from as early as 5 min into the dwell period. Whereas we used continuous measurement of haemodynamic variables, most published data concern intermittent measurement techniques. Therefore, although one study showed that an insulin infusion affected the HR as early as 10 min (which was the first data point recorded) [13], there are no other data revealing whether insulin can affect systemic haemodynamics even more acutely.

In our study, when comparing 1.36% glucose and icodextrin, we observed differences with a lower DBP and trend towards lower SV during icodextrin dwells. With regard to the relative amount of glucose in the two fluids, these differences may be less than expected, although some authors have found minimal effects on systemic haemodynamics with lower amounts of glucose and insulin. This raises the possibility of ‘dose–response’ or ‘threshold’ effects and that the amount of glucose absorbed is important in determining the magnitude of hyperinsulinaemia and haemodynamic response.

Three of our study patients were type II diabetics, two on insulin and one on sulfonylurea treatment. These patients were not analysed separately due to small numbers, but the patient on sulfonylurea treatment appeared to behave in a similar fashion to non-diabetics. The two patients on insulin treatment, however, did not display higher SV and CO during 3.86% glucose dwells. It is possible that the patient on sulfonylurea treatment had some degree of preserved residual insulin secretion to explain the changes in haemodynamics, although without further work measuring glucose and insulin levels in addition to haemodynamics this is conjecture.

Other than the difference in glucose content, icodextrin contains lactate as a buffer whereas Physioneal® contains bicarbonate/lactate mix and has a neutral pH. It is therefore possible that the difference in lactate content or in intraperitoneal pH might be responsible for some of the observed difference in haemodynamic effects. However, this seems unlikely because there were still significant differences between 1.36 and 3.86% Physioneal®, which both have an identical buffer. Furthermore, there are no changes in systemic pH as a result of using either buffer system [19]. Another difference between the fluid types is the lower amounts of GDPs in icodextrin. Despite an extensive literature search, no published work on the potential haemodynamic effects of GDPs was found.

Small patient numbers may potentially limit our study. However, by providing data for each pulse wave, the Finometer offers extremely high resolution of data differences. This allows accurate detection of
even small degrees of change in any of the haemodynamic variables measured, and at least partially compensates for the effect of smaller sample size. Another potential weakness of our study is that we did not have access to serum insulin levels to measure alongside the haemodynamic parameters. However, to prove causality, in addition to measuring insulin levels during CAPD with hypertonic glucose dialysate. our study design determined that 1.36% glucose was always given before the 3.86% and icodextrin dwells, and this may make comparisons of data from the 1.36% glucose dwells with 3.86% glucose and icodextrin less robust. However, it has been shown that the time of day does not affect the haemodynamic response to a carbohydrate load [20].

In conclusion, these data demonstrate that CAPD is associated with significant haemodynamic disturbance. We have also demonstrated that BP, HR, SV and CO are significantly higher during 3.86% glucose dwells compared with both 1.36% glucose and icodextrin dwells. BP measurements taken during 3.86% glucose dwells may therefore not be representative of overall BP. However, these results should be regarded as preliminary findings in view of the relatively small number of patients and short-term nature of the study. Although the mechanisms underlying the differences between dialysate types have not been elucidated, we suggest one explanation may be glucose absorption from peritoneal dialysate leading to hyperinsulinaemia, which then may affect systemic haemodynamics. Further studies are required to confirm our findings, investigate the underlying mechanisms and examine the long-term effects of adverse haemodynamics during CAPD with hypertonic glucose dialysate.

Conflict of interest statement. None declared.

References


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