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THE ADVANTAGE OF GLUCOSE POLYMER AS AN OSMOTIC AGENT IN CONTINUOUS PERITONEAL DIALYSIS

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Summary

The potential of starch-derived glucose polymer (MW 20,000) as an osmotic agent for peritoneal dialysis was evaluated. We compared dialysate containing 5% GPB (2.5mmol/L) with 1.36% glucose (76mmol/L) for ultrafiltration, solute clearance and absorption, during a single six hour dwell. The initial osmolality of GPB solution (304.7±4.2mOsm/kg) was lower than glucose solution (334±1.5mOsm/kg), yet the total ultrafiltration and average clearances for urea, creatinine, phosphate was greater. At the end of the exchange only 16 per cent of GPB in the dialysate was absorbed as compared to 64 per cent of glucose. There was a six-fold increase in serum maltose following GPB dialysis. This study suggests that GPB is a safe and effective osmotic agent. Its major advantages compared to glucose are sustained ultrafiltration, enhanced solute transport and potential reduction in calorie load.

Introduction

Major disadvantages of long-term continuous use of glucose on continuous ambulatory peritoneal dialysis (CAPD) are primarily related to rapid absorption through the peritoneum [1] resulting in ultrafiltration of short duration [2] and metabolic abnormalities such as hyperglycaemia, hyperinsulinaemia, hyperlipidaemia [3] and obesity [4]. These disadvantages could be minimized by the use of polymeric form of glucose. Glucose polymer, isolated by fractionation of hydrolysed corn starch, are a mixture of oligosaccharides of variable chain length, ranging from one to >30 glucose units, linked predominantly by 1–4 glucosidic and some 1–6 linkages. Their large size should limit the rate of absorption from the peritoneal cavity, thus producing sustained ultrafiltration. Any absorbed glucose polymer is rapidly hydrolysed to maltose (G_2) by amylase present in the circulation [5]. Maltase activity, however, is absent in human blood but significant quantities have been demonstrated in a variety of extra-

intestinal tissues [6], which are capable of metabolizing circulating maltose [7].

We studied previously a glucose polymer preparation (GPA) with an average MW 7000 (67% – 'low MW fraction' – containing 1 to 12 glucose units, MW 960; 33% – 'high MW fraction' – containing >12 glucose units, MW 19,000) which proved to be an effective osmotic agent but its use was limited by the rapid accumulation and persistence of maltose (G_2) in the blood [8].

We studied and compared a second glucose polymer preparation (GPB), weight average MW 20,000, with commercially available 1.36% glucose for ultrafiltration, solute transport, carbohydrate absorption and metabolism.

Subject and methods

We studied three non-diabetic patients (2 males, 1 female) aged 21–62 years (mean 36.7) who had been stable on CAPD for a mean period of 7.7 months (range 3–11 months). They were stabilized on four exchanges per day and had been free of peritonitis for at least three months prior to the study. Each patient underwent two separate six hour exchanges using two litres dialysis fluid containing either 1.36% glucose (76mmol/L) or 5% glucose polymer (2.5mmol/L).

After an overnight fast (10–12 hours), subjects were admitted to a hospital metabolic procedure room, dialysate was drained and two litres of fresh fluid were infused by gravity over 10 minutes. Blood and dialysate samples were taken simultaneously prior to dialysis and at 0, 15, 30, 60, 90, 120, 180, 240 and 360 minutes; time zero being the end of infusion. At the end of the six hour dwell, the fluid was drained and volume recorded. Normal dialysis schedule was resumed, except after the use of glucose polymer when the dialysis was discontinued for 24 hours and additional blood samples were taken at 3, 14 and 24 hours. Each study was separated by 48–72 hour intervals.

Assay methods

The serum and dialysate biochemistry was determined by Vickers M300 multichannel autoanalyser, glucose by glucose oxidase method, osmolality by the freezing point depression method and glucose polymer by Gel-permeation chromatography, on a Bio-gel P, using modified Jelco 6AH automatic carbohydrate analyser with orcinol-sulphuric acid detection system [9].

All values are expressed as mean ± standard error of mean (SEM).

Results

Ultrafiltration Net ultrafiltration, at the end of a six hour dwell, was greater with 5% GPB (407±2.2ml) compared to 1.36% glucose (200±107ml) solution.

Osmolality The initial osmolality of 5% GPB was considerably lower in comparison to 1.36% glucose solution (304.7±4.2 versus 334±1.5mOsm/kg). Figure 1 shows the relationship between dialysate osmolality and dwell time. The total dialysate osmolality for 5% GPB was moderately raised over the first three

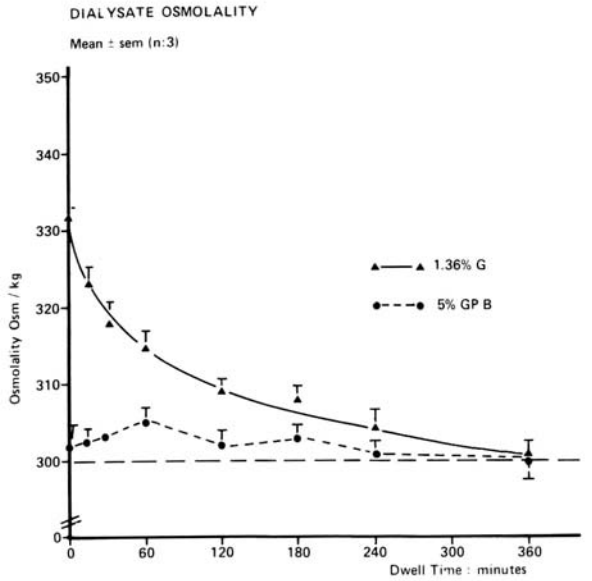

Figure 1. Relationship between total dialysate osmolality and dwell time

hours of dialysis before returning to pre-dialysis value, whereas rapid exponential decline was observed with 1.36% glucose.

Solute transport Table I shows the ratios of dialysate to plasma concentration (D/P) and average clearance values for urea, creatinine, phosphate and uric acid. Equilibration and clearances are both greater with 5% GPB solution for all solutes but the magnitude of this increase is particularly marked for those with larger molecular weights.

TABLE I. Equilibration (dialysate/plasma: D/P) and average clearance (mean ±SEM; n=3)

	D/P ratio % (6hr)		Average clearance – 6hr dwell (ml/min)		
Solute	G: 1.36%	GP: 5%	G: 1.36%	GP: 5%	% increase
Urea	93.8±3.3	99.4±2.8	6.24±0.11	7.02±0.19	12.5
Creatinine	77.0±3.2	97.3±1.9	5.29±0.16	6.16±0.14	16.4
Phosphate	70.0±3.7	80.2±2.4	4.66±0.23	5.58±0.14	16.5
Albumin	1.44±0.04	2.10±0.07	0.09±0.01	0.15±0.01	66.7

G=glucose; GP=glucose polymer

Carbohydrate absorption and metabolism At the end of the six hour dwell 18.9±2.0g of glucose polymer and 19.4±3.2g of glucose were absorbed representing 16 per cent and 64 per cent of initial carbohydrate load, respectively.

No appreciable changes in blood glucose were noted with either 1.36% glucose or 5% glucose polymer solution.

After six hour exchange with 5% GPB the serum maltose reached 0.22± 0.018g/L (0.6±0.05mmol/L), which is a six-fold increase when compared to pre-dialysis values. However this value is 77 per cent lower than previously observed (0.97±0.13g/L; 2.69±0.36mmol/L) following dialysis with 5% GPA (MW 7000) solution for a similar duration (Figure 2).

The clearance of serum maltose appears to be extremely slow in the absence of dialysis.

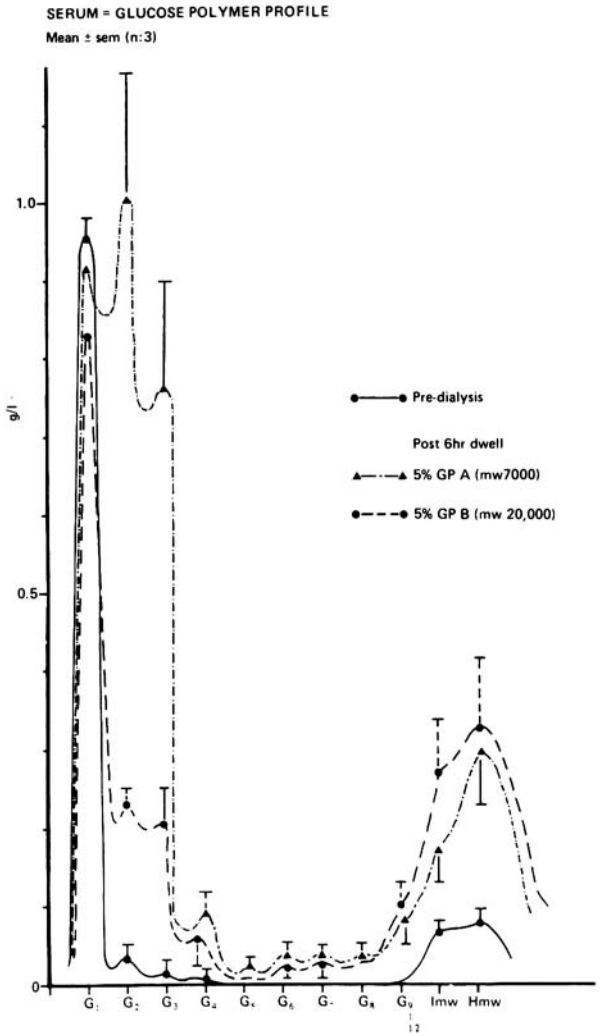

Figure 2. Serum glucose polymer profile, pre and post glucose polymer dialysis

Discussion

This study demonstrates that peritoneal dialysis fluid containing 5% GPB (2.86 mmol/L), which is virtually isosmotic to uraemic serum (302±0.7mOsm/kg), resulted in twice the ultrafiltration capacity compared to 1.36% glucose (76 mmol/L) solution of relatively high tonicity (332±1.0mOsm/kg). This phenomenon emphasizes the permeable nature of the peritoneum and the importance of molecular size in determining the direction and magnitude of osmotic flow through such a membrane. Whereas osmotic flow through a semi-permeable membrane is related to total number of solute molecules (total osmolality) irrespective of their size, flow through a more permeable membrane is only dependent on the number of large, relatively impermeable, molecules. Glucose polymer of large molecular size (high reflection coefficient) are less permeable than glucose (low reflection coefficient) through peritoneum and therefore maintain osmotic gradient for longer duration resulting in sustained ultrafiltration. Since the magnitude of osmotic flux through a permeable membrane is expressed by the product of the reflection coefficient of the solutes and its molar concentration, GPB are particularly effective even at low molar concentration. This is the physiological basis of 'colloid osmosis', similar to that induced by albumin across the capillary wall. The clinical application of this phenomenon to peritoneal dialysis has the considerable advantage of sustained ultrafiltration whilst maintaining dialysate osmolality near to the physiological range.

In addition a small but significant contribution to net ultrafiltration is made by the constant diffusion of serum glucose and maltose into the dialysate, along a concentration gradient, throughout the duration of an exchange. The osmolar concentration of these low molecular weight solutes more than compensates for the expected fall in osmolality, due to combination of dilution and some absorption of glucose polymer, resulting in a net increase in dialysate osmolality as observed in this study. Alternatively, intra-peritoneal breakdown of large glucose polymer fractions to smaller units could have a similar effect. However there is no evidence from the present study or in vitro experiments to support this view.

The limited absorption of GPB through the peritoneum has two major metabolic advantages. Firstly, the total amount of carbohydrate absorbed over a period of a six hour exchange is lower than with glucose solution (18.9 versus 19.4g). Secondly, absorbed polymers do not influence serum glucose or insulin, even when the systemic load is four to five times greater than achieved in this study [5,8].

The absorbed glucose polymer fractions are rapidly hydrolysed to maltose by circulating amylase. In our previous study, using 5% GPA (MW 7000), up to a 30-fold increase in serum maltose (0.97±0.13g/L) was observed [8]. This is drastically reduced to 0.22±0.018g/L, which only represents a six-fold increase, with present formulation (5% GPB). Although the half-life of maltose in renal failure is prolonged [8,10], continuous peritoneal dialysis will lead to a steady state level in the serum. No data are available on the long-term effect of maintaining such levels.

Some increase in average clearance of solutes is to be expected because of the greater convective transport associated with the superior ultrafiltration of GPB solution, but this does not explain the magnitude of enhanced equilibration observed for all solutes. It is likely that other mechanisms such as vasodilatation of peritoneal vasculature or increased peritoneal membrane permeability also operate. Assessment of mass transfer area coefficient (MTAC) of these solutes would clarify this point.

It must be emphasized that there has been no adverse effect observed with the use of GPB solution, apart from transient infusion associated abdominal pain lasting 20 minutes in one patient.

We conclude that a solution of glucose polymer (average MW 20,000) is a safe and effective osmotic agent with sustained ultrafiltration and superior solute transport characteristics to 1.36% glucose, while maintaining relatively low but stable dialysate osmolality. The reduced carbohydrate load associated with its use is an important metabolic advantage. Long-term studies will determine the future of this formulation in CAPD.

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References

1 Nolph KD, Twardowski ZJ, Popovich RP, Rubin J. *J Lab Clin Med 1979; 93:* 246
2 Pyle KW, Moncreif JW, Popvich RP. In Moncreif JW, Popvich RP, eds. *CAPD Update.* Paris: Masson. 1981: 32–35
3 Ramos JM, Gokal R, Siamopolous K et al. *Q J Med 1983: 52:* 165
4 Gokal R, Ramos JM, McGurk JC et al. In Gahl GM, Kessel M, Nolph KD, eds. *Advances in Peritoneal Dialysis.* Amsterdam: Excerpta Medica. 1981: 430–433
5 Bibby RJ, Davies D, Mallick NP et al. *Br J Nutr 1977; 38:* 341
6 Weser E, Sleisenger MH, Dickstein M et al. *J Clin Invest 1967; 46:* 499
7 Young JM, Weser E. *J Clin Invest 1979; 50:* 986
8 Mistry CD, Mallick NP, Gokal R. *Perit Bull 1984; suppl 4:* S42
9 Kennedy JF, Fox JE. In Whistler RL, BeMiller JN, eds. *Methods in Carbohydrate Chemistry Vol VIII 1980:* 13–19
10 Ohneda AS, Yamagata S, Tsutsumi K, Kujiwara H. *Tohoku J Exp Med 1974; 112:* 141