Carbohydrate and lipid metabolism during continuous ambulatory peritoneal dialysis (CAPD): the effect of a single dialysis cycle

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Summary

1. The effect on hormonal status and intermediary metabolism of a single 6 h dialysis cycle at two different concentrations of dialysate glucose was investigated in six patients on continuous ambulatory peritoneal dialysis.

2. The basal blood glucose level was elevated by 0.5 mmol/l, associated with a threefold increase in basal serum insulin compared with seven normal controls. Blood glucose and serum insulin rose further during dialysis, particularly with hypertonic (215 mmol of glucose/l) dialysis fluid and levels remained high for 6 h after the onset.

3. Plasma glucagon concentrations were 2.7-fold increased and did not decrease to normal during dialysis.

4. Concentrations of the gluconeogenic precursors lactate and alanine were consistently raised, and levels of circulating non-esterified fatty acids and ketone bodies were lowered, particularly with hypertonic dialysis fluid.

5. The long-term effects of sustained hyperinsulinaemia, including suppression of lipolysis and ketogenesis, require further investigation.

Key words: carbohydrate metabolism, glucose absorption, ketogenesis, lipolysis, peritoneal dialysis.

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; NEFA, non-esterified fatty acids.

Introduction

Uraemia is commonly associated with disturbances of carbohydrate metabolism. Intolerance to oral or intravenous glucose occurs in more than half the population with end-stage renal failure [1, 2], although fasting hyperglycaemia is less common [2, 3]. The hyperinsulinaemia associated with glucose intolerance has been attributed to peripheral insulin resistance [4] and recently to a post-receptor-binding defect [5]. Inappropriately raised levels of circulating glucagon [6, 7] and human growth hormone [8] have long been recognized.

Partial reversal of these abnormalities has been demonstrated after efficient haemodialysis [9, 10] and intermittent peritoneal dialysis [11]. By contrast, peritoneal dialysis may also induce certain abnormalities such as hyperglycaemia and hyperosmolality [12] as a result of glucose absorption from the dialysis fluid.

Continuous ambulatory peritoneal dialysis (CAPD) was first described in 1976 [13] and is now an established method of treating chronic renal failure [14]. Approximately 75% of the dialysate glucose is absorbed in CAPD [15], which, in patients using four 2 litre exchanges per day, amounts to a daily intake of between 80 g and 250 g of glucose over and above dietary consumption. Two possible consequences of a chronic high carbohydrate intake are obesity and hypertriglyceridaemia, both of which have been described in uraemia [16, 17] and in patients on CAPD [18, 19]. Such effects are important for the long-term well-being of patients on CAPD and may even limit the use of this form of dialysis. We have therefore studied the effect on various parameters of carbohydrate and lipid metabolism of a single
Methods

Subjects and protocol

Six uraemic patients, four males and two females, aged 30-65 years (mean 46 years) were studied. All patients had been established on CAPD for over 3 months and had been free of peritonitis within 1 month of any study. No patient was taking any drug known to affect carbohydrate metabolism (Table 1). All patients were performing four 2 litre exchanges a day, using Dianeal 137 (Travenol Laboratories, Thetford, U.K.). The glucose (anhydrous dextrose) concentration of the fluid was either 76 mmol/l (1.36 g/dl) (isotonic) or 215 mmol/l (3.86 g/dl) (hypertonic) and, in addition, contained Na 132 mmol/l, Cl 112 mmol/l, Ca 1.75 mmol/l, Mg 0.75 mmol/l and lactate 35 mmol/l. All patients had been advised to take a high protein (1.2 g/kg) diet and their normal daily intake was assessed, by 3 day recall, before these studies. In practice, the patients had a mean daily protein intake of 1.1 g/kg body weight and mean daily energy intake of 1900 kcal (range 1605-2050 kcal), with 44% derived from carbohydrate, 40% from fat and 16% from protein. All had normal serum values for bilirubin, liver transaminase and alkaline phosphatase. Seven normal subjects, four males and three females, aged 22-61 years (mean 39 years) were also studied. None was known to have disease or to be taking any medication. All subjects were within 10% of ideal body weight and were asked to eat a diet containing at least 250 g of carbohydrate daily for 3 days before each study.

The CAPD patients were studied on three separate occasions after a 10 h overnight fast. The last exchange was performed at 22.00 hours with isotonic (76 mmol of glucose/l) dialysis fluid and patients attended at 08.00 hours before the morning exchange. The patients remained recumbent and fasting throughout the study and blood samples were taken from an indwelling intravenous cannula, kept patent by intermittent flushing with NaCl (154 mmol/l). Dialysate was drained and an exchange performed using isotonic or hypertonic dialysis fluid, 2 litres over 10 min. In a third study, no exchange was performed and the patient remained drained of fluid throughout the period of investigation. Blood samples were taken at -15, 0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300 and 360 min, time zero being halfway through infusion of the fresh dialysis fluid.

dialysis cycle in patients established on CAPD, in order to clarify its metabolic consequences.
The three studies were performed in random order and at least 2 weeks elapsed between studies.

Normal subjects were studied after a similar overnight fast. Thirty minutes after insertion of the intravenous cannula, blood samples were taken at the same time intervals as for uraemic subjects. Subjects remained recumbent and fasting throughout the study. The study was approved by the Ethical Committee of the Newcastle Health Authority and informed consent was obtained from each subject.

Assay methods and analysis

Blood for determination of glucose, lactate, pyruvate, alanine, glycerol, 3-hydroxybutyrate and acetoacetate was taken into 5 ml of chilled HClO₄ (500 mmol/l) and assayed by an automated fluorimetric enzymic method [20] or, for acetoacetate, by manual spectrophotometric assay [21]. Blanks were run for all metabolites to take account of increased non-specific fluorescence in uraemic serum. Serum insulin was assayed by double-antibody radioimmunoassay [22], glucagon by C-terminal specific radioimmunoassay [23] and non-esterified fatty acids (NEFA) by a radiocobalt technique [24], and triglyceride as glycerol after hydrolysis [25].

Statistical analysis was by analysis of variance and, as appropriate, by paired or unpaired Student's t-test. Correlations were sought by linear regression analysis.

Results

Glucose, insulin and glucagon (Fig. 1)

Mean basal glucose levels in CAPD patients were 0.5 mmol/l above that of the normal controls and fell slowly with starvation. After dialysis, peak levels were reached by 45 min and were 7.2 ± 0.8 mmol/l (mean ± SEM; range 5.8-9.4 mmol/l) during hypertonic and 5.6 ± 0.2 mmol/l during isotonic dialysis (P < 0.05). Glucose levels remained significantly raised 6 h after the onset of hypertonic dialysis.

Basal insulin levels were high in uraemic subjects. After the use of hypertonic dialysis fluid (215 mmol of glucose/l) insulin levels rose in parallel with the glycaemic response, to reach a peak at 45 min. Levels fell slowly and remained significantly raised when compared with those in undialysed uraemic patients after 6 h. The insulin response was significantly greater with hypertonic than with isotonic dialysis.

Basal glucagon levels were also high in the CAPD patients. Although concentrations were marginally lower over the period of dialysis with the hypertonic solution, levels remained elevated throughout the study, compared with control subjects. Basal glucagon and insulin concentrations correlated significantly with each other in the CAPD subjects (r = 0.86, P < 0.05), but neither correlated with values for plasma creatinine, urea, haemoglobin, residual renal function, fasting triglyceride or blood glucose.
Lactate, pyruvate and alanine (Fig. 2)

The behaviour of these three gluconeogenic precursors was similar. Basal lactate levels in CAPD were high and the values remained elevated throughout, especially during hypertonic dialysis. Levels in fasting CAPD patients fell towards normal after 6 h. Basal pyruvate levels were not significantly different between uraemic patients and normals, but values became elevated during hypertonic dialysis. The lactate/pyruvate ratio was normal and did not alter in these experiments. CAPD was associated with elevated alanine concentrations throughout the three studies, particularly with hypertonic dialysis.

Ketone bodies (Fig. 3)

Basal ketone body (3-hydroxybutyrate and acetoacetate) concentrations were decreased in CAPD patients and rose in parallel with those of normal subjects on starvation. With hypertonic dialysis, levels remained markedly suppressed throughout the study period, and less marked changes were noted during the isotonic cycle. Similar changes were observed when 3-hydroxybutyrate and acetoacetate concentrations were considered alone. The 3-hydroxybutyrate/acetoacetate ratio was significantly lower in CAPD subjects than in controls throughout all three studies.
Glycerol and NEFA (Fig. 3)

Basal NEFA levels were low in CAPD patients and significantly lower levels were maintained during hypertonic dialysis. Circulating glycerol levels did not differ significantly from those in controls, but during hypertonic dialysis, glycerol, NEFA and ketone body concentrations correlated significantly with each other when both basal and mean levels over hypertonic dialysis were considered.

Discussion

Patients on CAPD dialyse for 24 h a day, 7 days a week, and treatment may continue for several years. The effect of absorption of substrates from the peritoneal cavity is therefore of some importance. The basal blood glucose concentration in the present study was elevated. This may have been related to the renal failure itself or, more likely, may have been due to continued absorption of glucose from the previous dialysis overnight. Absorption of glucose in CAPD is passive and depends on the gradient between dialysate and blood. Thus absorption is fairly predictable [15] and is rapid at the start of the dialysis cycle, then slows down as the dialysate glucose concentration falls. However, glucose absorption continues for 6 h, especially if fluid of high concentration is used [26]. The regular use of hypertonic dialysis fluid, to control fluid balance, is required by the majority (90%) of Newcastle patients on CAPD [19]. A 6 h cycle with a dialysis fluid containing 215 mmol of glucose/l results in the absorption of about 305 mmol (55 g) of glucose [15, 26]. The prolonged effect of this slow absorption means that CAPD patients are never truly starved and that there is a continuous stimulus to insulin secretion.

Furthermore, the metabolic fate of the absorbed glucose is uncertain. Oral glucose is absorbed actively from the gut and it has been calculated that 90% appears in the systemic pool within 4 h of ingestion [27]. The insulin response is enhanced after oral, as opposed to intravenous, glucose [28] due to stimulation of gastrointestinal hormones [28, 29]. Equivalent data for glucose absorbed from the peritoneal cavity are not available. The hyperinsulinaemia, both basal and in response to fresh dialysis, presumably reflects both renal failure itself [2, 3] and the additional glucose load.

Lactate and pyruvate levels are not increased by uraemia per se [30]. Lactate absorbed from the dialysis fluid may contribute to the higher lactate levels during peritoneal dialysis. Lactate absorption should, however, be independent of the dialysate glucose concentration and amount to less than 30 g/day in our patients [31]. This can be set against an estimated daily endogenous production of 120 g/day and maximum utilizing ability of 330 g/day [32]. None of our subjects had any evidence of liver disease, the liver being the main organ of lactate utilization [32, 33]. In the present study, lactate levels were highest with 215 mmol of glucose/l dialysis fluid, suggesting that the raised levels most likely result from an increase in endogenous production by glycolysis, coupled with reduced utilization by gluconeogenesis. Both these effects may be mediated by the raised ambient insulin levels. Pyruvate and lactate are in equilibrium and changes in pyruvate therefore follow changes in lactate concentration. Although these changes probably reflect increased insulin effect, they are of no immediate pathological significance, as lactic acidosis will not occur until levels rise above 5 mmol/l [33]. Alanine is the main protein-derived precursor for gluconeogenesis and is in equilibrium with pyruvate. Rubenfeld & Garber [34] have shown that alanine production and utilization are increased in uraemia. This occurs despite hyperinsulinaemia and, in the present study, levels may have increased further as a result of the increase in circulating lactate, with which it is in equilibrium.

Other changes may also be related to hyperinsulinaemia. A previous report of low levels of NEFA in uraemic patients during an oral glucose tolerance test was attributed to inhibition of lipolysis secondary to hyperinsulinaemia [35]. This effect was also noted in these studies, although changes in blood glycerol were less impressive. The reduced ketone body levels are also likely to be secondary to the insulin-induced decrease in NEFA substrate supply. This sensitivity to the action of insulin on fatty acid and ketone body metabolism is in contrast to the resistance to the peripheral action of insulin on glucose [5] and amino acid uptake [36].

The glucagon antiserum employed was C-terminal specific and therefore believed to measure only the pancreatic hormone, although interference by non-active, 9000 daltons glucagon may occur. The incomplete suppression with hyperglycaemia suggests abnormal regulation of glucagon secretion and has previously been noted with oral glucose [6].

Although glucose absorption with CAPD can occasionally be useful in providing an important source of calories for some uraemic patients who are ill and malnourished [26], the hyperinsulinaemia associated with constant glucose absorption may in the long term have unwanted effects, and may possibly increase atherogenesis [37] in patients
who are already exposed to raised levels of triglyceride and lipoprotein remnants [38, 39]. Only long-term studies on cardiovascular morbidity and mortality in patients on CAPD will determine its effect on the development or progression of arterial disease.

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References