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5. Carbohydrates

METHODS

Literature Search

Medline search, Pub-Med search.

Timeframe: publications from 1983 to February 2004.

Type of publications: e.g. *original papers, meta-analyses and overviews.*

Key Words: children, PN, Glucose, carbohydrate, energy-resource, insulin.

Language: English and French.

CARBOHYDRATES

Introduction

Carbohydrates are the main source of energy in nutrition and usually provide 40–60% of the energy supply in western diets. The majority of the carbohydrate derived from a normal diet reaches the body's peripheral tissues as glucose. Glucose is utilised by all cells and serves as metabolic fuel for muscle, liver, heart, kidneys and gut and as the obligate energy source for brain, renal medulla and erythrocytes. Glucose is the main carbohydrate utilised during foetal life; about 7 g/kg per day (approximately 5 mg/kg per minute) of glucose crosses the placenta in the last trimester of pregnancy.

The major source of non-protein calories in parenteral nutrition (PN) is D-Glucose (dextrose), which is provided in the monohydrate form for intravenous use. Dextrose usually contributes most of the osmolality of the PN solution.

By considering the consequences of excessive glucose intake during PN, and by taking into account the rate of glucose production and oxidation, it is possible to establish recommendations. Energy provision during PN includes the use of intravenous fat emulsions (IVFE) (see Lipids chapter). IVFE provide a concentrated source of calories with a low osmotic load (2.0 kcal/ml for a 20% emulsion, compared to about 0.8 kcal/ml for a 20% dextrose solution). The optimal glucose/lipid ratio remains to be defined. Glucose tolerance may be influenced by cyclical PN, metabolic status, acute illness and always requires careful monitoring.

Consequences of Overfeeding with Glucose

In the past, PN for adults, children and infants provided most of the energy as glucose, although it was not precisely known how much of the intravenously-administered glucose was oxidized.

When glucose is administered in excess of the amount that can be directly oxidized for energy production and glycogen, the excess is directed to lipogenesis thus promoting fat deposition (1,2). Restoration of fat stores may be a nutritional goal in patients with severe malnutrition, however excessive fat deposition may be deleterious. Whatever the situation, this conversion into lipids accounts, in part, for the increase in energy expenditure observed with high rates of glucose infusion (3).

Excessive glucose intake is thought to increase CO2 production and minute ventilation but few relevant data are available to support the clinical relevance (4–6). Total energy delivery as well as amino acid intake also contribute to increased CO2 production and minute ventilation (5,6).

Excessive glucose intake may also impair liver function especially by inducing steatosis, while its contribution to the development of cholestasis is not clearly established (7–9). Studies in normal adult volunteers suggest that high carbohydrate feeding leads to an increase in total VLDL triglyceride secretion rate from de novo synthesis, primarily due to stimulation of the secretion of preformed fatty acids (FA) (10). These results imply that the liver derives it's energy from carbohydrate oxidation rather than from FA oxidation, while FA taken up by the liver are channelled into VLDL triglycerides (10). Hepatic steatosis results when export of the VLDL triglycerides does not keep pace with triglyceride production (10,11). PN may be associated with insulin resistance, due to both the substrate infusion and the underlying disease (12,13).

Protein metabolism is influenced by the composition of energy intake in patients on PN (14–17). Lipid emulsion allows the energy input to be diversified, with a reduction in the consequences of excessive glucose supply. In adults, as well as in paediatric patients, the use of IVFE and/or the reduced glucose intake was shown to improve net nitrogen balance (14–17).

PN is associated with an increased risk of infectious complications compared with enteral feeding or no nutritional support. The most recent and largest meta-analysis of 27 studies in 1828 adult surgical patients confirmed that enteral feeding does carry a lower infective risk than PN, but at the cost of a non-significant trend towards increased complications. Overall, enteral feeding did not reduce mortality compared to PN (18). However,

failure to prescribe PN for malnourished patients who are unable to tolerate enteral feeds triples their risk of death (19).

Animal data suggests that hyperglycaemia might be a risk factor for infection. Hyperglycaemia in an animal model reduces the ability of lung macrophages to fight infection (20). Animal data suggests that infection reduces non-hepatic glucose utilisation and causes hyperinsulinism (21). High blood glucose levels in adult ICU patients are associated with increased infectious-related mortality (22).

Statements

- Excessive glucose intake may be responsible for hyperglycaemia. **LOE 1**
- Excessive glucose intake causes increased lipogenesis and fat tissue deposition together with subsequent liver steatosis and enhanced production of VLDL triglycerides by the liver. **LOE 2-3**
- Excessive glucose intake causes increased CO2 production and minute ventilation. **LOE 3**
- Excessive glucose intake causes impaired protein metabolism. **LOE 2-3**
- High blood glucose levels have been shown, in adult ICU patients, to be associated with increased infectious-related mortality. **LOE 2-3**

Rate of Endogenous Glucose Production and Rate of Glucose Oxidation

The efficiency with which glucose is used to meet energy needs should guide its relative contribution to PN regimens. Exogenous glucose delivered in excess of the rate of glucose oxidation may enter non-oxidative pathways and is unlikely to improve energy balance.

The majority of quantitative estimates of production and oxidation of glucose have been performed using stable isotopic tracers and indirect calorimetry in newborns, while only few studies are available for infants and children. Basal rate of glucose production (RGP) varies from 2 mg/kg per min in adults, to 8 mg/kg per min in preterm infants (or from 3 g/kg per day to 11.5 g/kg per day) (23–26). The RGP is maximal during the post natal period and decreases gradually with age.

Gluconeogenesis provides a significant amount of glucose, and is responsible for about 31% rate of glucose appearance in healthy full term newborns (23). A clinical trial of 20 preterm infants on PN (25) showed that these infants maintain normoglycaemia by glucose produced via gluconeogenesis as a result of glycerol delivery from fat metabolism. This suggests that not all the glucose has to be provided exogenously (25).

During PN, the rate of parenteral glucose delivery must be kept constant without exceeding the maximum rate of glucose oxidation (RGO), which differs significantly among patients according to their age and clinical status. During high rates of glucose infusion, there is a complete suppression of endogenous production of glucose, accompanied by hyperinsulinism and a respiratory quotient equal to 1.0. A linear relationship was shown in newborns between glucose intake and glucose utilization, measured by indirect calorimetry and glucose oxidation measured by stable isotopic tracers (24).

In appropriate for gestational age-preterm infants, the RGO does not exceed 6 to 8 mg/kg per min (9.5 g/kg per day) after birth (27,28) while in term surgical infants or infants on long-term PN, the maximal RGO is about 12 mg/kg per min (18 g/kg per day) (29,30). A study in critically burned children, demonstrated the maximal RGO to be 5 mg/kg per min, which is below caloric requirements (31). The clinical approach is probably to exercise restraint in the delivery of glucose in critically ill children. While estimations of caloric requirement for children often include a component to support growth, this may not be a reasonable goal in a child receiving acute care for severe injury or illness. Except for preterm infants, one could consider that maximal RGO is continuously decreasing from birth to adulthood taking into account the brain to total body weight ratio and the brain glucose consumption.

Thus glucose intake should be adapted to age and clinical situation e.g. premature babies, infants and children, critically ill patients and severe malnutrition.

Statements and Recommendations

- Production of glucose varies from 2 mg/kg per min in adults to 8 mg/kg per min in preterm infants (or from 3 g/kg per day to 11.5 g/kg per day). **LOE 2**
- In preterm infants glucose infusion should be started with 4–8 mg/kg per min. **GOR C**
- Maximal glucose oxidation in preterm infants is 8.3 mg/kg per min (12 g/kg per day) after birth. **LOE 2-3**
- In critically ill children glucose intake should be limited to 5 mg/kg per min (7.2 g/kg per day). **GOR D**
- Glucose administration to full term neonates and children up to 2 years of age should not exceed 18 g/kg per day (13 mg/kg per min). **GOR C**
- Variations in glucose intake according to age and clinical situation (e.g. malnutrition, acute illness, drug administration) should be considered. **GOR D**
- Glucose intake should be adapted in case of simultaneous administration of drugs known to impair glucose metabolism such as steroids, somatostatin analogs, tacrolimus. **GOR C**
- The recommended glucose supply is shown in Table 5.1. **GOR D**

TABLE 5.1. *Recommended parenteral glucose supply (g/kg body weight and day)*

	Day 1	Day 2	Day 3	Day 4
Up to 3 kg	10	14	16	18
3–10 kg	8	12	14	16–18
10–15 kg	6	8	10	12–14
15–20 kg	4	6	8	10–12
20–30 kg	4	6	8	<12
>30 kg	3	5	8	<10

- These recommendations need to be adapted to the clinical situation (e.g. refeeding syndrome in severe malnutrition) to oral and/or enteral energy intake and to the required weight gain for normal or catch up growth. **GOR C**
- It is important, especially when prescribing PN for infants, to accurately evaluate the carbohydrate load provided by concurrent infusion therapy. **GOR C**
- In critically ill and unstable patients, it is reasonable to start with lower amounts of carbohydrates and increase the amounts according to the patient's condition. Metabolic complications associated with a more rapid introduction of carbohydrate may be uncommon in more stable patients, and this approach can be an exercised if blood glucose is closely monitored. **GOR C**

Glucose/Fat Ratio

Substitution of part of the glucose calories with fat derived calories avoids the undesirable effects reported with glucose-based PN. Studies performed in infants or neonates have assessed glucose and fat utilization (32–35). In infants, it was possible to study the optimal glucose infusion rate by using five isocaloric PN regimens differing in their glucose/lipid ratio (32). Fat infusion aiming at a significant contribution to the coverage of energy expenditure requires that glucose oxidation be equal to or lower than maximal oxidative glucose disposal. For maximal lipid infusion rates see chapter on Lipids.

Recommendation

- Glucose intake should usually cover 60–75% of non-protein calories. **GOR C**

Cyclical Parenteral Nutrition

The term cyclical PN refers to the administration of intravenous fluids intermittently with regular discontinuation of infusion (36). Most available data comes from studies performed in stable adult patients on long-term PN (37–40). Cyclical PN is well established with documented tolerance in children (41–44). However cyclical PN may lead to high glucose infusion rates with subsequent hyperglycaemia, and an increased risk of hypoglycaemia upon discontinuation.

In clinical practice, cyclical PN may be performed as soon as clinical status permits. Maximal glucose infusion rate should not exceed 1.2 g/kg per hour, and the rate of infusion should be increased in a stepwise manner. Such a stepwise adaptation of infusion rate will not only avoid glucose overload but also hyperosmotic load from electrolytes. A similar stepwise reduction of infusion rate is also recommended at PN discontinuation to avoid hypoglycaemia (45).

Advantages of cyclical PN include:

1. Alternating fasting and feeding periods allows for changes in the insulin/glucagon balance and reduces lipogenesis in both adipose tissue and liver.
2. Physical activity during the day that is beneficial for protein synthesis and growth as well as psychologic behaviour (46). In that regard, advantages in terms of nitrogen balance were never shown in the conditions of the experiments in humans.
3. Cyclic PN might lower the risk for the development of liver disease. In a prospective study (47), involving adults on PN exhibiting various degrees of presumed PN-associated liver disease, patients who developed hyperbilirubinemia were randomized to either remain on continuous PN or were placed on cyclic PN. Patients with initial serum bilirubin less than 20 mg/dl, who remained on continuous PN, had a significant rise in serum bilirubin compared with the cyclic PN groups. There was no apparent advantage of cyclic PN in patients with serum bilirubin greater than 20 mg/dl. Similar studies in paediatric patients are not available.

Recommendations

- Cyclical PN is well tolerated and may be used from 3–6 months of age. **GOR C**
- In cyclical PN the maximal rate of glucose infusion may exceed glucose oxidation rate. The maximal infusion rate should not exceed 1.2 g/kg per hour (20 mg/kg per min). **GOR C**
- A stepwise increase and decrease of glucose infusion rates at onset and at discontinuation of the infusion respectively should be considered to avoid hyper- and hypoglycaemia. Glucose tolerance should be monitored. **GOR D**

Monitoring and Use of Insulin

PN may be associated with insulin resistance, due to both the substrate infusion and the underlying disease. Animal studies suggest that a PN adapted state is reached

in long term PN, where liver glucose uptake is unresponsive to rises in insulin above basal level (21).

Particular attention must be paid to glucose tolerance (hyperglycaemia, glycosuria) at the time of starting cyclic PN, since decreasing the duration of infusion may lead to excessive increase in the glucose rate of delivery. Osmotic diuresis may cause water and electrolyte depletion. In patients on stable long-term PN, glycosuria may indicate a stressful event, particularly infection, which impairs sensitivity to insulin (48).

Some children receiving PN have abnormal glucose tolerance (13). Insulin secretion and sensitivity were measured in 12 patients; the insulin response to sustained hyperglycaemia was stronger in children with normal glucose tolerance while receiving cyclic PN. Two patients with abnormal glucose tolerance showed decreased capacity to release insulin. Whole body glucose disposal was greater in younger than older children (range 7.1–25.2 mg/kg per min) ($p < 0.01$) (13).

A study in adult ICU patients showed that by using insulin to control blood glucose between 80–110 mg/dl, mortality in the ICU was reduced from 8 to 4.6%, overall in-hospital mortality was reduced by 34% and bloodstream infections by 46% (49). The message in adults, in ICU, is to keep glucose infusion below 4 mg/kg/min and manage hyperglycaemia with insulin. However, these data have to be confirmed in children, and therefore no firm recommendation can be made. Also, pre-term infants given insulin respond variably to insulin and may develop profound hypoglycaemia.

Recommendations

- Hyperglycaemia causing marked glycosuria should be avoided. **GOR D**
- Hypoglycaemia (<2.5 mmol/l, [<50 mg/dl]) should be avoided. **GOR D**
- Insulin infusion may be used in VLBW infants with hyperglycaemia while on PN, but the safety and the effects on clinical outcome are presently unknown. **GOR D**
- The use of insulin should be restricted to conditions where reasonable adaptation of glucose infusion rate does not control marked hyperglycaemia. **GOR D**

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