Parenteral nutrition in pediatrics Indications and perspectives

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Parenteral nutrition (PN) since its introduction in clinical practice during the last sixties has allowed survival of many patients and has reduced the incidence of malnutrition related to a variety of digestive and non digestive diseases. With antibiotics, antitumoral chemotherapy and organ transplantation, PN can be considered as one of the most important therapeutic advances of the last 50 years. Technical aspects, psychological consequences of feeding "deprivation" and high rate of complications have leaded mistrust with respect to this therapeutic at the early phase of its development. Continuous clinical and basic research have allowed to improve its efficiency and to reduce the rate of complications. Now, parenteral nutrition has demonstrated its potential for changing the course of both medical and surgical patients. This short review will focus on the main indications of PN, some new data concerning PN substrates and prevention of PN-related complications (1, 2).

Indications for parenteral nutrition Digestive and extra-digestive indications

PN is indicated in children for correction or prevention of malnutrition, whatever the cause of malnutrition, as soon as it becomes impossible to use the enteral route. The range of these indications, involving both the gastrointestinal tract and other areas, has greatly increased during the last years. However, because of the iatrogenic risk of the technique, especially when it is used for several weeks, each indication should be discussed while PN should be, as often as possible, performed in specialized units, such as intensive care, hematology-oncology or gastroenterology units. The indications for PN may be divided into digestive and non-digestive pathology (Table I). Gastrointestinal (GI) indications for PN can be subdivided in three main situations : malabsorption syndromes, indications of bowel rest and congenital or acquired neonatal pathology of the GI tract.

Certain congenital or acquired metabolic diseases, such as severe hepatic or renal failure with Gl complications, can benefit from PN with appropriate AA solutions. An increasing area of use of parenteral nutrition is represented by the management of children with malignant disease. PN has changed dramatically the management of the oncological chemotherapy protocol (2). Parenteral nutrition can also be indicated as a nutritional supplement in end-stage liver disease, during the waiting period before orthotopic liver transplantation (3). The same is true in the severe phase of cystic fibrosis when lung transplantation is required (4). Sometimes PN may be the only way of maintaining an adequate nutritional intake even when the gastrointestinal tract is intact for example after multiple trauma or extensive burns. In these situations, parenteral nutrition may also be necessary to maintain nutritional status despite increased nitrogen catabolism or excessive nitrogen loss.

Long-Term Parenteral Nutrition and home parenteral nutrition

As soon as the metabolic and nutritional status permit, cyclic *PN* should be started. The advantages of cyclic infusion are metabolic, physical, and psychological. The tolerance of this mode of administration has been documented in children (5). In addition cyclic PN is the way in which home PN is used. Patients requiring long-term parenteral nutrition certainly need to be managed by a special center, from which a program of home PN can be organized (6). Nutrition is generally mixed parenteral and enteral, but it may be exclusively parenteral, lasting for months or years. Some indications are total or subtotal resection of the small intestine, syndromes of chronic intestinal pseudo-obstruction, refractory atrophies of the intestinal mucosa with severe, persistent malabsorption, either alone or in association with an immune deficiency, and certain cases of Crohn's disease that are extensive and/or have undergone multiple surgery, with growth retardation, or that have not responded to other therapy.

The objective of long-term PN in these cases is to ensure normal growth of the child while an inflammatory syndrome subsides or before a residual intestinal condition becomes stable. Whatever the duration of PN and whatever the prognosis, home PN offers a quality of life as close as possible to that of other children or adolescents of the same age (6, 7). In addition cost is reduced compared with hospitalization. Cyclic infusions, adequate and appropriate provision of macro- and micronutrients, and improvements in catheters and nutritional mixtures have all played a role in making home PN possible. The development of an infrastructure for patient training and follow-up, a PN solution

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factory unit, and an efficient domiciliary delivery service have also allowed home PN. Over the past 12 years, more than 250 children in our unit were able to remain at home on cyclic PN. Home PN indications were short bowel syndrome (40%), Crohn's disease (15%), chronic intestinal pseudo-obstruction (13%), and intractable diarrhea of infancy (7%). Growth and quality of life were good in most cases. Forty-five percent of the patients are no longer on home PN, 40% are still on home PN, and 15% have died from the underlying disease. These results as well as those of other teams suggest that home PN seems to be the best option for children in need of long-term PN. Ethical dilemnas may arise with children with massive gastrointestinal resection, microvillus inclusion disease or persistent villous atrophy who will never be able to tolerate full enteral feeding. Indeed in such patients in whom intestinal autonomy will never be achieved, intestinal transplantation may represent the logical therapy (8).

Adaptation of parenteral intake and new substrates

Optimal glucose-fat ratio

For a long time, TPN for infants and children provided most of the energy as glucose, although it was not precisely known how much of the IV-administered glucose was oxidized. Glucose-based TPN has been shown to cause an adverse effect related to glucose storage, particularly as fat. This might account for the extensive lipid deposition reported both in liver and adipose tissue (9). In these conditions, fat infusion further increases fat deposition and may result in fat overloading. Thus, substitution of part of the glucose calories avoids the undesirable effects reported with glucose-based TPN. In addition it has been shown by several authors that the use of IVFE improves nitrogen retention (10, 11). Recent studies performed in infants or neonates have assessed glucose and fat utilization and have determined the optimal lipid intake (12-14). 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. Hence glucose infusion rates should be lower than 18 g/kg/day (12). A study in malnourished infants and young children has shown a maximal lipid utilization rate of about 3.3.-3.6. g/kg/day (14). Above these values there is an increased risk of fat deposition secondary to the incomplete metabolic utilization of infused lipid. Pierro showed similar results in a short-term study performed in surgical neonates on TPN (13). Finally, short-term as well as longterm lipid use must be included in all TPN programs in infants and children. Lipid infusion rate must be below 3.5 g/kg/day representing up to 30% of nonprotein energy intakes. A slow infusion rate, such as 0.1-0.2 g/ kg/h, allows the best metabolic utilization, and may avoid fat overload and reticulo endothelial system involvement (15).

New intravenous fat emulsions

IVFE containing medium-chain triglycerides (MCT) are now widely used in adult and pediatric patients. MCT are oxidized when used as a calorie source. Fatty acids from the hydrolysis of MCT are the primary substrate for ketogenesis. Carnitine is needed to transport long-chain fatty acids into the mitochondria, but malnourished and seriously ill patients may be carnitine depleted (16). An energy source able to bypass this route into the mitochondria would in theory, be useful for such patients. One recently available lipid emulsion containing MCT contains 50% long-chain triglycerides to avoid any possible side effects from excessive quantities of MCTs and to provide EFA. Medium-chain fatty acids can enter the mitochondria by simple diffusion, independent of the carnitine enzyme and produce an elevation of plasma ketones (17). MCTs have been shown to improve nitrogen balance in post-operative patients (18). At the present time there have been several published studies on children using MCT (19). Our experience with it in malnourished infants after 15 days on TPN indicates that it is well tolerated and could provide advantages in terms of nitrogen metabolism by supplying the equivalent of 25% non-protein energy intake (20). MCTs emulsion have been used in home TPN pediatric patients (21). Other source of triglycerides are currently under development. One is a newly developed pediatric fat emulsion containing only long-chain triglycerides with 15% of the fat content provided by borage oil as source of γ-linolenic acid (22). On the other hand, a high intake of monounsaturated fatty acids in the form of olive oil is associated with a lower incidence of cardiovascular morbidity. New 20% fat emulsions containing 17% olive oil and 3% soybean oil will be available for pediatric patients within the next few months (23). Finally, to improve the safety and the efficiency of MCT-containing fat emulsions and to circumvent their disadvantages, a structured triglyceride emulsion, containing both long-chain and medium-chain fatty acids bound to the same carbon skeleton, has been synthetized. Such structured triglyceride emulsions have been shown to improve nitrogen retention and muscle protein synthesis in animal model (24).

Nitrogen sources

Protein energy malnutrition secondary to chronic disease as well as acute illness such as injury or infection are associated with the loss of body fat and skeletal-muscle mass. The loss of body tissue may be minimal and of little consequence in patients with normal nutritional status and a brief, self-limiting illness lasting few days. On the contrary, when the disease is prolonged and the patient is malnourished, a variety of clinical events may occur in association with catabolic state. These alterations include immunosuppression, delayed wound healing and tissue repair and loss of muscle strength. The accelerated breakdown of body protein

can be slowed by the administration of adequate quantities of energy, protein (amino acids), and other essential nutrients. However, measurements of body composition and substrate-flux studies indicate that it is extremely difficult to maintain or replenish body protein during catabolism. Thus, reducing the debility associated with catabolic process could potentially enhance recovery and decrease the consequences of illness on protein retention and height growth velocity. Because the efficacy of nutrition cannot be easily improved by quantitative modifications, attention has focused in the recent years on qualitative improvments. The addition of specific amino acids or other source of nitrogen to the feeding formulas might be logical in critically ill children (sepsis, burns,trauma) or in patients with chronic inflammatory process such as severe Crohn's disease.

Nitrogen source available for parenteral nutrition comes from various mixtures of crystalline L-amino acids. They have been shown to be effective in clinical use providing appropriate nitrogen utilization and retention. New paediatric solutions have been developed which appear to be better suited for use in newborns, premature babies or malnourished infants (Primene, Clintec® ; Vaminolac, Pharmacia®). Glutamine (Gln) being the most abundant aminoacid in the body (25), is absent from the currently available aminoacids solution. Gln is considered as unstable in aqueous solutions and during heat sterilization with the formation of pyroglutamic acid and ammonia. Although Gln is a non essential amino acid, studies in animals indicate that the nutritional requirement for this amino acid during catabolic illness may differ greatly from those during health. During starvation or stress, the concentration of free Gln in the intracellular amino acid pool of skeletal muscle rapidly decreases. Gln exported from the muscle is used primarily by visceral organs ; in the kidney, it serves as an ammonia donor, in the gastrointestinal tract, it serves as a primary oxidizable fuel source for enterocytes and colonocytes (26, 27). Gln also supports other rapidly proliferating tissue, such as fibroblasts or lymphocytes. Gln-supplemented total parenteral nutrition has been shown to preserve gut structure and to improve gut immune function in animal models (28). Recent studies have shown the clinical benefits of Gln-supplemented TPN in adult patients undergoing bone marrow transplantation (29-31). The use of Gln-containing dipeptides is proposed regarding the instability of free Gln. Improved nitrogen balance have been shown in patients receiving alanyl-glutamine supplemented TPN (32). In addition, Gln dipeptide-supplemented parenteral nutrition prevents intestinal atrophy and increased permeability in critically ill adult patients (33).

An other source of nitrogen for patient on parenteral nutrition is represented by ornithine α-keto glutarate (OKG). This is a salt formed with two molecules of ornithine and one molecule of α-ceto-glutarate. OKG has been sucessfully used by the enteral and parenteral route in burn, traumatized and surgical patients and in chronically malnourished patients. According to the situation, OKG administration decreases muscle protein catabolism and/or increases protein synthesis. The mechanism of action of OKG is not fully understood, but it was clearly demonstrated that it is aprecursor of Gln (34, 35). In addition, the secretion of anabolic hormones (insulin, human growth hormone) and the synthesis of metabolites (polyamines, arginine, ketoacids) may be involved (36). In prepubertal children on parenteral nutrition, administration of OKG (15gr/day) reversed growth retardation and increased IGF-1 plasma levels (37). Finally it seems likely that in the near future more specific therapeutic approach of protein metabolism might be achieved. This perspective is of great importance for children regarding the consequences of inadequate protein metabolism on growth velocity.

Prevention of complications

Catheter Monitoring

Sepsis is one of the most serious complications which can arise during parenteral nutrition, and the use of a CVC undoubtedly increases the risk of infection (38). A two years prospective study of 185 CVCs showed a sepsis rate of 0.26%, with an overall incidence of 1 catheter related sepsis per 278 days of TPN (39). Systemic antibiotics provided sepsis control in 88% of the cases while CVC removal was required in the other cases. The factors significantly correlated with sepsis were : age (1-5 years) ; CVC type (surgically inserted CVC were more frequently infected) ; local haemorrhage following CVC insertion ; and local suppuration at the skin exit site. Prevention of catheter-related sepsis requires strict asepsis during both CVC insertion and changes of filter and infusion sets. Daily care of the CVC skin exit site is of great importance (40). All PN solutions must be prepared under a laminar flow hood and filtered. The care of the child should be undertaken by physicians and nurses who have been specifically trained in this technique. Fever or clinical signs suggestive of catheter-related sepsis should lead to a thorough search for a source of sepsis, together with a white blood cell count, C-reactive protein and coagulation tests. Samples for blood culture should be taken via the catheter and from a peripheral vein. If the body temperature remains elevated, antibiotic therapy should be started, using antibiotics against Staphylococcus. Removal of the catheter is not considered unless the PN programme is close to completion, and in other cases it can only be considered if the patient continues to deteriorate even when appropriate antibiotic therapy had been started. With good technique, displacement or obstruction of the catheter, or thrombosis of the superior vena cava are rare. Careful technique should also help prevent superficial venous

thrombophlebitis and the risk of dissemination of septic emboli.

Parenteral nutrition related bone disease

The so-called PN related bone disease resembles rickets, with fractures of the limbs which are sometimes asymptomatic and are only discovered after routine X-ray examination (41, 42). The most constant laboratory features are an elevated alkaline phosphatase activity and hypercalciuria, with normal or subnormal levels of vitamin D metabolites and parathyroid hormone. Bone histology shows osteomalacia-like changes with reduced mineralization and excess of osteoid tissue. The aetiology of these bone lesions is probably multifactorial : excess vitamin D or disorders of its metabolism mean that it must be given very carefully on long-term parenteral nutrition. It is also possible to reduce the hypercalciuria by ensuring that the supplies of phosphorus, nitrogen and energy are properly balanced, while reducing the supply of amino acids, especially the sulphur-containing amino acids. Finally, it is necessary to ensure that the solutions used for children on long-term parenteral nutrition are not contaminated with aluminium (43). Prevention of this "bone disease" depends primarily on regular measurements of urinary calcium, which should not exceed 5 mg/kg per 24 h, and serum alkaline phosphatase activity (44).

Parenteral nutrition related liver disease

Hepatobiliary complications are frequently observed during long-term parenteral nutrition. They are well recognized and documented (45, 46). Such liver involvment may result in some cases in end stage liver disease within a few months or years. Many factors are involved in these hepatobiliary complications. The underlying disease plays a prominent role especially in case of short bowel syndrome with ileum resection suppressing enterohepatic cycle of biliary acids. Bowel rest required by GI disease suppress or reduce biliopancreatic and digestive secretions. Recurrent septic episodes either catheter related (gram positive bacteria) or digestive related (gram negative sepsis from intraluminal bacterial overgrowth) cause liver injury. Several other factors are directly related to parenteral nutrition such as amino acid contain of PN solutions, aluminium overload, excessive glucose intake and EFA deficiency. Steatosis with clinical liver enlargement may appear within a few days after the start of parenteral nutrition. The first and most sensitive laboratory indications are increases in alkaline phosphatase and gamma-glutamyl transferase activities. An increase in transaminase activity is also an early and specific sign, but it is less sensitive. Steatosis is the first histological manifestation, followed by cholestasis and portal and periportal cell infiltration. Hepatic fibrosis indicates severe liver disease, but is fortunately rare if parenteral nutrition is performed correctly. It is extremely important to monitor hepatic function in order to minimize factors responsible for liver disease, such as EFA deficiency, or excess dextrose. The amino acid solutions used should be safe and appropriate to a paediatric population. Certain measures have been found to limit liver disease :

1. Stimulation of the enterobiliary axis by ingestion of long-chain triglycerides or breast milk, or by injection of cholecystokinin analogs
2. Suppression of intraluminal bacterial overgrowth stasis by giving metronidazole or antibiotic coktail
3. Use of soxycholic acid
4. By decreasing aluminium content of parenteral nutrition solution
5. By limiting glucose intakes to reduce hepatic fat accumulation
6. Use of IVFE which provides essential fatty acids and reduce glucose load
7. Use of pediatric amino acid solutions providing appropriate amount of amino-acids and taurine
8. Cyclic PN may contribute to a decrease in hyperinsulinism and reduce in liver steatosis

Conclusion

PN has become a widely used therapeutic. Nevertheless it should be reserved to appropriate indications and avoided each time the enteral route is able to ensure adequate nutritional intakes for correction or preventionof malnutrition. The deployment of a multidisciplinary nutrition support team minimizes inappropriate or unadapted prescription of PN. In case of protracted intestinal failure and PN requirement, home-PN has to be considered in order to improve the quality of life.

Table I. — **Indications for parenteral nutrition**

Digestive indications
Malabsorption medical and/or surgical
Protracted and intractable diarrhoea
Short bowel syndrome
Enterocutaneous fistula
Proximal enterostomy
Intestinal bacterial overgrowth
Immune deficiency
Indication of bowel rest
Inflammatory bowel disease (Crohn, ulcerative colitis, unidentified colitis)
Necrotizing enterocolitis
Intestinal lymphangiectasy
Acute pancreatitis
Gastric hypersecretion
Systemic disease : Shonlein-Hennoch, periarteritis
Radiation enteritis
Congenital or acquired neonatal pathology of the GI tract
Gastroschisis
Omphalocele
Meconial ileus
Extensive small bowel resection

Necrotizing enterocolitis
Complicated Hirschsprung disease
Chronic intestinal pseudo-obstruction syndrome

Extra-digestive indications

Neonatology : premature baby 1500 g

Metabolic disease

— End-stage liver disease
— Congenital disorders of metabolism
— Cystic fibrosis

Hematology and oncology

— Solid tumours
— Leukaemia
— Bone marrow transplantation

Nephrology

— Severe renal disease
— Severe tubulopathy
— Renal failure

Hypercatabolism

— Burned
— Polytraumatism
— Surgery

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