Nutritional Therapy & Metabolism / Vol. 24 no. 3, pp. 120-126 Wichtig Editore, 2006

Review Article

TPN-related digestive alterations. Animal and human data in the non-critical setting

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ABSTRACT: In TPN-fed animals the lack of enteral nutrition (EN) induces significant and early alterations in gut mucosal morphology, crypt cell proliferation, and sugar and amino acid absorption. Both changes in gut mucosal immunity (reduction of total lymphocytes and bile secretory IgA, impairment of mitogenic response of gut lymphoid populations) and loss of respiratory immunity have been documented. In addition, an imbalance between Th2 IgA stimulating cytokines and Th1 IgA inhibiting cytokines has been observed; this imbalance upregulates the inflammatory response in the intestine and other organs. Intestinal motility, bacterial ecosystem and blood flow are also affected by TPN: the duration of MMC is prolonged; cecal and ileal bacterial content is greatly increased and both portal and superior mesenteric artery blood flows are decreased by 30% after 8 h of TPN. In humans the available data are remarkably less. Fourteen days of TPN in healthy volunteers induce a significant decrease in mucosal thickness and in the number of villous cells, while crypt cells are unaffected. No remarkable alterations in cell proliferative activities have been reported, except in subjects affected by inflammatory bowel diseases. Alterations in immunity (decrease of IgA immunocytes) have been clearly demonstrated only in infants and children on TPN, while in adults the TPN-induced changes in intestinal immunity may only be suggested on the basis of speculative considerations. The minimum enteral feeding that can protect the gut integrity has been indicated in rats (20-25% of the caloric requirement to reduce bacterial translocation) and in piglets (40-80% to maintain proliferative and functional gut activities). (Nutritional Therapy & Metabolism 2006; 24: 120-6)

KEY WORDS: TPN-related intestinal alterations, Gut mucosal immunological impairement, Intestinal permeability, Intestinal motility

INTRODUCTION

In this paper experimental and human studies on intestinal alterations during total parenteral nutrition (TPN) in the healthy state or in non-critical diseases are reviewed. The vast majority of the information summarized below has been derived from animal models and relatively little information is available from human studies.

TPN has been associated with changes in gut morphology, intestinal blood flow and several intestinal functions such as cell proliferation and apoptosis,

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enzymatic functions, immune defence, permeability, barrier integrity, motility, and bacterial ecology.

It has not been clearly defined whether intestinal changes are determined by the absence of luminal nutrient substrates or by TPN itself. The question has been addressed by a recent study in a mouse model where it has been demonstrated that it is the lack of enteral feeding rather than TPN that increases apoptosis of epithelial cells, changes phenotype and functions of intraepithelial lymphocytes and causes bacterial translocation (1).

Changes in gut mucosal morphology

Animal data

It has been demonstrated (2, 3) that rats receiving 10-15 days of TPN exhibit, compared with a control group fed by chow, a significant ($p < 0.001$) decrease in jejunal mass, jejunal and ileal length of villi (2), and in perimeter length, mucosal thickness, villous area and villous surface in the distal ileum (3). Recent studies in a model of neonatal piglets have shown that the gut alterations occur very early: by day 3 ileal crypt depth, and by day 7 both jejunum villous height and crypt depth were found significantly lower ($p < 0.05$) in TPN vs TEN fed animals (4); in similar experimental conditions Burrin et al (5) demonstrated that, after 6 days of TPN, a significant ($p < 0.001$) decrease in the small intestinal weight and in the protein and DNA content of small intestinal mucosa occurs, while Niinikoski et al (6) were able to show that similar changes (decrease in total mucosal intestinal weight and in jejunal mucosal weight and DNA mass, villous height, protein mass, crypt cell proliferation and mean number of crypt cells) occur even after 48 h of TPN. They also observed a higher rate of apoptosis in both the crypt and villi ($p < 0.05$); interestingly, it was shown that these changes are preceded by portal venous and superior mesenteric arterial blood flow suppression, which occurs rapidly (within 8 h) after TPN; within 24 h of TPN, inducible nitric oxide synthase decreases and mucosal atrophy occurs. The authors suggest that the insufficient supply of oxygen and nutrients to villous epithelial cells may induce hypoxia, oxidant stress, and eventually cell death and villous atrophy.

In *human studies* TPN-induced gut alterations were less marked and not consistently detected: no significant changes in villous height were observed in patients fed by TPN for 10 d before surgery (7), while in healthy volunteers 14-d TPN was associated with a significant decrease in mucosal thickness ($p < 0.003$) and in the number of villous cells ($p < 0.03$); however, the number of crypt cells and the microvillous height were not significantly affected (8).

Changes in digestive, absorptive and proliferative functions of the epithelial cells

Animal data

Niinikoski et al. (6) were able to show, in the jejunum of neonatal piglets and compared to EN, that 24h TPN results in significant decrease in both protein fractional synthesis and crypt cell proliferation ($p<0.05$); these changes continue to progress after 48 h. Burrin et al (5) studied in infant pigs the effects of 6-d TPN, compared to EN: in animals pre-treated with TPN they observed a marked reduction in the net absorption of both glucose and galactose and a significant, but less pronounced, suppression of the absorption of lysine, threonine, isoleucine and arginine; the arterial utilization and oxidation of leucine were also significantly lower. Therefore, it is possible to conclude that in infant animals TPN induces early and relevant alterations in functional and proliferative activities.

In Table I the results observed in human studies are reported: conclusions cannot be drawn, due to the heterogeneity of the clinical situations in which the studies have been performed; it could be hypothesized that in humans the lack of EN might damage the functional and proliferative activities only when TPN is administered in subjects with a concomitant inflammatory status of the digestive tract (9, 10, 12), or in long-term TPN (11), while no alterations are induced by short-term (12-14 d) TPN in adult healthy subjects (8) or after neurosurgery (12) and by medium-term (30 d) TPN in IBD children (11).

Changes in gut mucosal immunity and intestine-derived inflammatory responses

Most of the knowledge derives from experimental studies, which enable to separate the effects of malnutrition on gut immunity from those related to EN deprivation.

Animal studies

It has been demonstrated that, in mice, both TPN and the intragastric infusion of the same TPN bags, compared to complex enteral diet (CED) and chow, induce, in the entire small intestine, up to 50% overall reduction in total lymphocytes (T and B cell population) both in Peyer's patches and in lamina propria, together with a significant reduction in CD4+ cells and in the

TABLE I - ENZYMATIC AND PROLIFERATIVE ACTIVITIES DURING TPN. HUMAN STUDIES

Author	No. of Patients	Duration of TPN	Observations
Guedon C, 1986 (9)	7 IBD adult pts	21 days	↓ enzymatic activities of the brush border ($p < 0.05$) ↓ peptidases ($p < 0.05$)
Inoue Y, 1993 (10)	6 pre-operative adult pts	7 days	↓ brush border transport of aminoacids (except that of glutamine) by 26%-44% ($p > 0.05$) ↓ brush border transport of glucose ($p > 0.05$)
Rossi TM, 1993 (11)	3 IBD children (9-17 yrs)	1 month	- disaccharidase activities: non significant changes
	4 SBS children (7-54 months)	> 9 months	↓ disaccharidases ($p < 0.05$) ↓ thymidine incorporation ($p < 0.001$)
Wicks C, 1994 (12)	24 adult pts after liver transplant	10 days	↓carbohydrate absorption ($p < 0.05$)
Buchman AL 1995 (8)	8 healthy adult volunteers	14 days	- disaccharidase activities: non significant changes
Suchner U, 1996 (13)	34 adult pts after neurosurgery	12 days	↓ vitamin A absorption ($p < 0.05$) - d-xylose absorption : non significant changes - lactose tolerance : non significant changes

IBD= Inflammatory Bowel Disease
SBS= Short Bowel Syndrome

CD4:CD8 ratio in lamina propria (14); these changes occur rapidly, reaching a maximum within three days of TPN (15), and in the same short time are reversed by the resumption of the chow diet (16). It was also shown that TPN impairs the mitogenic responses of the gut lymphoid populations (17), and decreases the number of bile secretory IgA, IgA plasma cells in terminal ileum (18) and the overall secretion of intestinal IgA (14); a parallel reduction of respiratory mucosal IgA was also documented (15), demonstrating that the lack of luminal nutrient stimulation of the gastro-intestinal (GI) tract may cause an extraintestinal suppression of the mucosal immunity. The enteral stimulation of the GI tract is also essential to maintain the pre-established respiratory mucosal immunity against viruses and bacteria: 50% of TPN-fed mice lost the pre-acquired protection against APR/8 *Haemophilus* influenza virus, while all animals fed via the GI tract were able to clear it (19); similarly, after immunization with *Pseudomonas* antigen, five days of TPN induced a loss in respiratory immunity to the bacterial challenge, while animals fed by chow or by CED maintained it intact (20).

The TPN-induced reduction in the lamina propria CD4:CD8 ratio (20) leads to a change in the balance that under normal conditions is maintained between Th2 IgA stimulating cytokines (IL-4, IL-5, IL-6, IL-10 and IL-13) and Th1 IgA inhibiting cytokines. The lack of enteral feeding reduces the former and has no effect on the latter (21); this imbalance accounts for approximately 50% of the drop in IgA and upregulates the inflammatory response in the intestine and other organs: it has been observed that TPN induces a significant increase in the expression of intercellular adhesion molecule-1 (ICAM-1) in both intestine and lung (22), of P-selectin in the intestine and of E-selectin in the pulmonary vasculature (23), in conjunction with increased intestinal levels of myeloperoxidase, a marker of polymorphonuclear neutrophil accumulation. These phenomena have been hypothesized to act as a diet-induced "first hit" to the intestine, which in turn can affect the response to subsequent insults like ischemia/reperfusion. Actually, mice pre-treated with TPN had 80% mortality after 30 minutes gut ischemic insult, while 10-15% mortality was observed in chow and CED-fed animals (24).

Human studies

In adults, two weeks of TPN in healthy volunteers did not affect intestinal immune function, measured by the number of IgA-, IgM- and IgG-producing cells, T and B cells, and the intraepithelial and lamina propria lymphocyte counts (25). In a recent meta-analysis on clinical studies, in which EN was compared to PN, Braunschweig et al. (26) found that tube feeding was associated with a lower risk of infection than was PN, and the effect remained in the subgroup analyses for the presence of cancer, nutritional status, year of study

publication and study-quality score. The results of the metanalysis do not enable to establish if EN has a specific protective role on mucosal immunity, which in any case cannot be excluded; however, the higher rate of infection of TPN, which persists even after removing the effect of catheter sepsis, seems to result, at least in part, from factors specifically related to TPN, like hyperglycemia.

It has been documented that in human infants there is a reduction in intestinal IgA immunocytes when parenteral feeding was initiated (27); in children, a 50% decrease in IgA immunocytes has been observed in defunctioning colostomies within 2 to 11 months of surgery (28).

In conclusion, there is no doubt that in animals the lack of EN is associated with derangements of intestinal and extraintestinal immunity; in adult humans, the effect has not been clearly demonstrated, even though EN is associated with a lower risk of infection than PN; in infants and children the lack of EN induces a decrease in IgA immunocytes.

Changes in intestinal permeability; bacterial translocation

Several experimental studies have demonstrated that TPN alters intestinal permeability, while bacterial translocation (BT: the passage of intact, viable bacteria from the intestinal lumen to the mesenteric lymph nodes) has been variably pointed out. In humans, elevation in gut permeability has been frequently, but not always, found; however, in the one study that addressed the question (7), it was observed that BT is unaffected by TPN. Moreover, O'Boyle and coworkers (29) did not find any relationship between BT and neither the intestinal permeability NOR the index of villous atrophy. In Table II the results of experimental and human studies are reported.

Changes in intestinal motility

The effect of TPN has been studied experimentally in dogs, using both regimens containing only glucose and amino acids (38) and the usual clinical solutions of glucose, amino acids and lipids (39). It has been shown that both TPN regimens did not alter phase III of migrating motor complex (MMC) neither in one site of jejunoileum (38) nor at the midpoint of the duodenum, at the jejunum 10 cm distal to the ligament of Treitz, at the midpoint of the small intestine between jejunum and ileum, and at 15 cm proximal to the ileocolic junction (39); moreover, the transit time during fasting has been found unaltered (38). However, during complete TPN, the duration of MMC was prolonged, and the occurrence of phase III reduced, in the stomach, duodenum and gallbladder; in both stomach and duodenum a prolongation of phase II was also observed (39). In humans, it has been clearly demonstrated that

TABLE II - INTESTINAL PERMEABILITY AND BACTERIAL TRANSLOCATION DURING TPN. EXPERIMENTAL AND HUMAN STUDIES

Author	Animals/ Patients	Duration of TPN (days)	Method (for gut permeability)	Intestinal permeability	Bacterial translocation
Experimental studies					
Alverdy JC, 1988 (30)	Rats	14		n.a.	+
Illig KA, 1992 (2)	Rats	10	lactulose	+	n.s.
Haskel Y, 1994 (31)	Rats	7		n.a.	+
Mosenthal AC, 2002 (32)	Rats	7	Ex-vivo using chamber system	+	+
Kansagra K, 2003 (33)	Piglets	6	Mannitol, lactulose, PEG 4000	+	n.s.
Zengh YJ, 2004 (34)	Rats	7			+
Human studies					
Van der Hulst RRW, 1993 (35)	IBD, cancer	10-14	Lactulose/mannitol	+	n.a.
Buchman AL, 1995 (8)	Healthy volunteers	14	Lactulose/mannitol	+	n.a.
Sedman PC, 1995 (7)	Pre-op	10			n.s.
Carr CS, 1996 (36)	Post-op	6	Lactulose/mannitol	+	n.a.
Reynolds JV, 1997 (37)	Post-op	7	Lactulose/mannitol	ns	n.a.

n.a.= not available
n.s.= no significant difference from control
IBD= inflammatory bowel disease
Pre-op= pre-operative period of gastrointestinal surgery
Post-op= post-operative period of gastrointestinal surgery

gallbladder motility is impaired by complete TPN (40, 41). IV glucose reduces gastric motility; the inhibitory effect is related with the degree of hyperglycemia and may result from the suppression of the activity of the vagal-cholinergic nerve system and the reduction of motilin (42). Lipid infusion causes gastric emptying delay (43), and, at high infusion rate, reduces the occurrence of phase III in the jejunum (44). However, IV administration of high doses of amino acids (AAs) stimulates gastric acid secretion (45) and gallbladder contraction (46); both effects are antagonized by the concomitant infusion of glucose (47) and lipids (45). During infusion of AAs, the intestinal transit time is significantly prolonged, the reoccurrence of phase III was accelerated and phase II was suppressed (48).

Changes in intestinal bacterial ecosystem

Several studies in rats have demonstrated that, after 7-10 d of TPN, cecal (2, 31), and ileal (49) bacterial content greatly increases, while only minimal changes are observed in jejunum (49). The increase is completely represented by anaerobes and gram-negative enterics. In TPN-fed piglets, it has been observed that the ileum content of bacteria that grew rapidly with mucin (mucin-associated bacteria), and in particular that of *Clostridium perfringens*, is significantly higher than that of TEN-fed animals (50). *Clostridium perfringens* is an opportunistic pathogen possibly contributing to necrotizing enterocolitis in low-birth-weight infants, to infectious diarrhea and to enteritis necroticans.

Changes in blood flow

Interestingly, a recent study in 3-week-old piglets has demonstrated that after 8 h of TPN both portal and superior mesenteric artery blood flow decrease by 30% compared with enteral feeding; this change precedes the morpho-functional alterations that appear after 24 h (villous atrophy and the suppression of protein synthesis) and after 48 h (decrease in cell proliferation and rise in apoptosis) from the onset of TPN (6).

How much is the "minimum enteral feeding"?

It has been claimed that a low quantity of enteral feeding protects the gut from the TPN-dependent alterations. Experimental studies in rats have shown that bacterial translocation decreases progressively with the increase in oral feeding; a percentage of 20-25% of the calories given as chow is considered sufficient to reduce to a safe level (~10%) the number of bacteria-positive mesenteric lymph nodes (51, 52), while the same amounts do not improve intestinal permeability and immunity (52, 53). However, higher enteral intakes are necessary in piglets to increase jejunum protein mass and villus height (> 40%), and ileal protein mass (> 60%), to sustain normal mucosal proliferation and growth (> 60%) and to increase total lactase activity both in proximal jejunum and ileum (> 80%) (54).

CONCLUSIONS

There is no doubt that the lack of enteral feeding is associated with alterations in intestinal integrity and functions; they occur early and may severely influence morbidity and mortality in experimental animals. In humans, the intestinal changes are fewer, appear later and seem to be particularly associated with acute and post-traumatic conditions. Most of all, TPN-related risks depend on its complications. Presently, TPN can be considered as a safe and beneficial method of feeding, if based on proper indications and undertaken by experienced teams.

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Received: June 6, 2006
Accepted: July 6, 2006