Clinical Significance of GLP-2 in Short-Bowel Syndrome

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ABSTRACT

Although long-term parenteral nutrition is lifesaving in patients with intestinal failure, it is expensive, severely impairs the quality of life in the short-bowel patients and is associated with serious complications such as catheter sepsis, venous occlusions and liver disease. Therefore, treatments that aim to minimize intestinal absorption, thereby eliminating or minimizing the need for parenteral support, are needed. As a result, glucagon-like peptide 2 (GLP-2) has received attention. In this review, the nature of short-bowel syndrome is described and the antisecretory, transit modulating and intestinotrophic effects of GLP-2 are presented. As illustrated in a pilot study, GLP-2 may prove to be important in the attempt to optimize remnant intestinal function thereby eliminating the need for parenteral support and improving quality of life in short-bowel patients with intestinal failure. J. Nutr. 133: 3721–3724, 2003.


Short-bowel syndrome, intestinal insufficiency and failure

The gut has two principal functions: absorption of fat, carbohydrates and protein to meet the metabolic needs of the body, and absorption of wet weight and electrolytes, mainly sodium, to avoid dehydration and electrolyte depletion. Short-bowel syndrome refers to an aggregation of clinical signs and symptoms primarily caused by intestinal resection and subsequent malabsorption characterized by intractable diarrhea, dehydration, malabsorption of macronutrients, weight loss, malabsorption of vitamins and trace elements and malnutrition. Intestinal insufficiency refers to the impairment of intestinal absorption that may be compensated for by hyperphagia (1–3), physical or metabolic adaptation, whereas intestinal failure ensues when parenteral support (fluids and/or energy), is necessary to maintain nutritional equilibrium, body composition, function and health. Factors influencing prognosis after massive small bowel resection are the length of the bowel resected, the site of the small bowel resection, the presence or absence of the colon and the function of the residual bowel. There are two common types of patients with short bowel: those with mainly jejunum remaining and those with jejunum in continuity with the colon. Balance studies have demonstrated that intestinal failure may be defined by measurements of wet weight and energy absorption. In general patients who absorb <1.4 kg/d of wet weight or <84% of their calculated basic energy needs according to the Harris Benedict equations depend on parenteral fluid or energy support, respectively (4). Frequently, this is a patient with <50–70 cm of small bowel, if the colon is intact, or <100–150 cm small bowel, if the resection is associated with a colectomy (5–8).

Intestinal adaptation

The term “intestinal adaptation” may be applied to the progressive recovery from intestinal insufficiency or failure that follows the loss of intestine. Figure 1 illustrates the theoretical possibilities of intestinal adaptation following intestinal resection. A “spontaneous adaptation” or recovery of intestinal function is generally described, reaching plateau at a certain time. When trying to improve intestinal adaptation, therapies could lead to either reaching a higher plateau phase (“hyperadaptation”), or reducing the time period until the plateau is reached (“accelerated adaptation”). The time issue may be relevant in patients who are difficult to maintain on parenteral nutrition. When trying to wean stable patients from parenteral support the aim is to achieve maximum functional absorptive capacity obtained by hyperadaptation and represented by the level of the plateau.
Hormonal control of intestinal adaptation

The search for specific hormones related to intestinal adaptation occurring after resection has been intensive. Control of the intestinal function is complex and influenced by both feed-forward and feed-back mechanisms that may be disturbed after intestinal resection (9). A number of pathophysiological abnormalities in short-bowel syndrome may in fact be caused by a malfunction of these regulatory control mechanisms that normally secure adequate intestinal digestion, absorption and motility.

With the finding of the "intestinotrophic" properties of GLP-2 by Drucker et al. (10), this hormone has received attention as a therapeutic agent in the treatment of short-bowel patients (11,12). GLP-2 is secreted from the intestinal L-cells mainly located in the ileum and colon. It has been speculated that L-cells, through the secretion of proglucagon-derived peptides, may serve as sensors in the distal intestine providing feedback information to the upper intestine in order to optimize nutrient and fluid absorption. Thus, increasing loads of nutrients or fluid into the ileum and colon may stimulate the secretion of glicentin, oxyntomodulin, GLP-1 and GLP-2. Whereas the biological activity of glicentin and oxyntomodulin remains controversial (13), GLP-1 is a intestinotrophic hormone (14,15) that also inhibits gastric secretion and motility by inhibiting central parasympathetic outflow (16). In addition to mediating increased jejunal absorption through induction of jejunal epithelial proliferation, GLP-2 has been shown to slow gastric emptying (17), increase intestinal transit time and inhibit sham feeding-induced gastric acid secretion (18). Administration of a potent protease-resistant analogue of GLP-2 has been demonstrated to augment the adaptive response to massive intestinal resection in rats (19), and postsectional intestinal growth correlates to circulating GLP-2 levels (20). The finding of an impaired meal-stimulated GLP-2 response in short-bowel patients with a jejunostomy (21), and an increased meal-stimulated GLP-2 secretion in short-bowel patients with a preserved colon, combined with the knowledge of the antisecretory (18) and transit modulating effects of GLP-2 (17), could explain why short-bowel patients with an intact colon show improved absorption with time, whereas patients with jejunostomy do not (22). This prompted Jeppesen et al. to investigate the effect of exogenous GLP-2 administration in short-bowel patients with a jejunostomy (23). Eight patients were treated with 400 μg of glucagon-like peptide-2 twice a day given subcutaneously for 35 d in an open label study. Four patients with a mean residual jejunum of 83 cm received intravenous nutrition, whereas four patients with a mean ileum resection of 106 cm did not. The patients were considered to be in a stable phase, 4-17 y from their last intestinal resection and none of the six patients with Crohn's disease had signs of active disease. Seventy-two-hour balance studies were performed, biopsies taken from jejunal/ileal stomas, transit measured by scintigraphy and body composition by dual-energy X-ray absorptiometry. Furthermore, the meal-stimulated GLP-2 response was measured after a standard test meal. As expected, none of the patients studied had a preserved meal-stimulated GLP-2 response. The maximum increase in the GLP-2 concentration following meal stimulation was only 9 pmol/L, comparing with a mean increase of 44 pmol/L (range, 1-77 pmol/L) in healthy controls (21). In comparison, supraphysiological plasma GLP-2 concentrations of 420-1240 pmol/L were obtained 30 min after the subcutaneous injections of 400 μg GLP-2.

Treatment with GLP-2 increased energy absorption by 3.5 ± 4.0% from 49.9 ± 20.3% to 53.4 ± 18.1% (P = 0.04) equivalent to an increase of 13.1 ± 22.3% of the absorption at baseline (49.9%). Absorption of carbohydrates improved by 0.35 ± 0.44 MJ/d (P = 0.06), which was borderline significant, whereas the relative absorption showed a nonsignificant increasing trend of 4.4 ± 7.5% (P = 0.14) from 69.7 ± 22.0% to 74.1 ± 15.9%. Excretion of protein (nitrogen) decreased 0.14 ± 0.13 MJ/d (P = 0.02), but the effect on the absolute absorption did not reach statistical significance (P = 0.16). This was in contrast to the improvement in the relative absorption of protein that increased by 4.7 ± 5.4% from 47.4 ± 29.3% to 52.1 ± 28.4% (P = 0.04). The effect of GLP-2 on fat absorption was negligible. Thus, the increase in fat absorption of 1.3 ± 8.0% (P = 0.66) from 26.9 ± 16.8% to 28.2 ± 19.8% was not significant. The improvement in the amount of energy absorbed was obtained in spite of a nonsignificant decrease in intake of 0.17 MJ/d, which means that the reduction in the energy malabsorbed (equal to the stomal excretion) was proportionally larger at 0.62 MJ/d.

Treatment with GLP-2 also had a considerable effect on wet weight absorption, which increased from 25 to 36%, a gain of 0.42 kg/d due to an improvement from 1.21 to 1.63 kg/d. Correspondingly, stomal outputs decreased by 0.49 kg/d, which was a remarkable effect in steady state patients already optimally treated by conventional medication.

Several physiological mechanisms possibly account for the effects of GLP-2. GLP-2 may diminish gastric acid secretion as demonstrated in sham feeding of healthy humans (18). However, the largest effect on intestinal wet weight absorption (0.82 and 1.25 kg/d, respectively) was in fact demonstrated in the two patients already treated with a combination of the antisecretory agents, omeprazole and octreotide, which may render this explanation less attractive. Another important difference to conventional antisecretory treatment was that GLP-2 improved both wet weight and energy absorption in contrast to H2-receptor antagonists and proton-pump inhibitors that have no effects on energy absorption in patients with intestinal resection (24). GLP-2 prolonged gastric emptying of solids whereas gastric emptying of liquids was prolonged in all but one of the patients. However, the combined gastric emptying and small...
bowel transit time was not changed by GLP-2, and small bowel transit time consequently tended to decrease. Hence, the effect of GLP-2 on transit time in short-bowel patients was complex and it is not clear if this effect plays a role in the improved absorption of energy and wet weight.

It is believed that the intestinotrophic effect of GLP-2 is responsible for a part of its effect on intestinal absorption but statistical analysis in the limited number of patients failed to provide sufficient proof. Morphometric analysis showed that villus height and crypt depth increased in six and five of the eight patients, respectively, which on an average was increased by 18% and 10%, respectively.

The nutritional benefits of increased intestinal absorption in short-bowel patients should preferably be reflected in changes of body weight and composition. Thus, the increases in the body weight and lean body and bone mass, and the reduction in fat mass seen as a result of the 5-wk treatment with GLP-2, were taken as clinical indications of a beneficial effect, which most probably was mediated through the effect on intestinal absorption. In addition, the increase in urine creatinine and the absence of clinical signs of edema supported that the increase in lean body mass, as measured by dual-energy X-ray absorptiometry, actually reflected an increase in muscle mass. The observed increases in serum albumin and sodium were also encouraging.

The dose of GLP-2 and the duration of therapy in the study of Jeppesen et al. were chosen arbitrarily. The optimal duration and concentration requirements for GLP-2 to induce beneficial effects on intestinal secretion, motility, morphology and most importantly absorption, are not known. Future studies have to show if more frequent administration, a higher dose or a longer duration of treatment with GLP-2 further improve the effects on intestinal function. Development of GLP-2 analogues characterized by a prolonged release or a slower degradation (25) may also be an interesting approach to improve the effect. The clinical effects of such treatment have only been described in abstract form. ALX-0600, a dipeptidyl peptidase-IV resistant GLP-2 analogue administered for 21 d, resulted in a reversible increase in crypt/villus architecture and mucosal cell number. There was a dose-dependant increase in RNA concentration, and a decrease in protein concentration per cell. Clinically, this led to an increase of the intestinal wet weight absorption of 614 ± 306 g/d (P < 0.02), whereas the effect on intestinal energy absorption did not reach statistical significance in 10 jejunostomy patients with intestinal failure.

CONCLUSIONS
Currently, hormonal therapy in short-bowel patients should be considered experimental and it is only recommended in research studies. The results of balance studies may identify those patients with severe malabsorption that are likely to have irreversible intestinal failure and those whose balance is “borderline” in whom hormonal manipulation or dietary therapy may “rehabilitate” short-bowel patients, eliminating or reducing the need for parenteral supplements. The optimal duration and concentration requirements for GLP-2 to induce beneficial effects on intestinal secretion, motility, morphology and most importantly absorption, are not known. Optimal dosage and administration of this new treatment to short-bowel patients may eventually result in long-term improvements in nutritional status and independence of parenteral nutrition in a larger fraction of short-bowel patients. This may improve the overall quality of life in these patients. Due to the difficulties of balance studies, weaning from parenteral support has been introduced as the sole endpoint after introduction of new treatments. This cannot be recommended because the parenteral support can be reduced in all patients on home parenteral nutrition for shorter or longer periods. Therefore, before introduction of new treatments, we recommend highly controlled short-term balance studies in which the true need for parenteral support is objectively measured and the effects of the interventions are given. These should be followed by evaluations of the effects of treatments in the everyday settings of the patients. Positive effects of hormonal interventions on intestinal wet weight and energy absorption may be demonstrated in short-term experiments in which the diet intake is fixed. However, changing the diet or introducing hormonal agents with negative effects on satiety may lead to a decrease in the overall spontaneous dietary intake, thereby jeopardizing the overall effect. Focus should also be addressed to the undesirable effects of interventions and with the introduction of growth factors on possible long-term complications.

LITERATURE CITED


