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(54) **TREATMENT OF SHORT BOWEL SYNDROME PATIENTS WITH COLON-IN-CONTINUITY**

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A61K 38/18 (2006.01)
A61K 35/38 (2006.01)

(52) **U.S. Cl.** **530/308**; 514/2; 424/551

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Intestinal absorption is enhanced in short bowel syndrome patients presenting with colon-in-continuity by treatment with a GLP-2 receptor agonist, such as teduglutide.

18 Claims, 2 Drawing Sheets

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Figure 1.

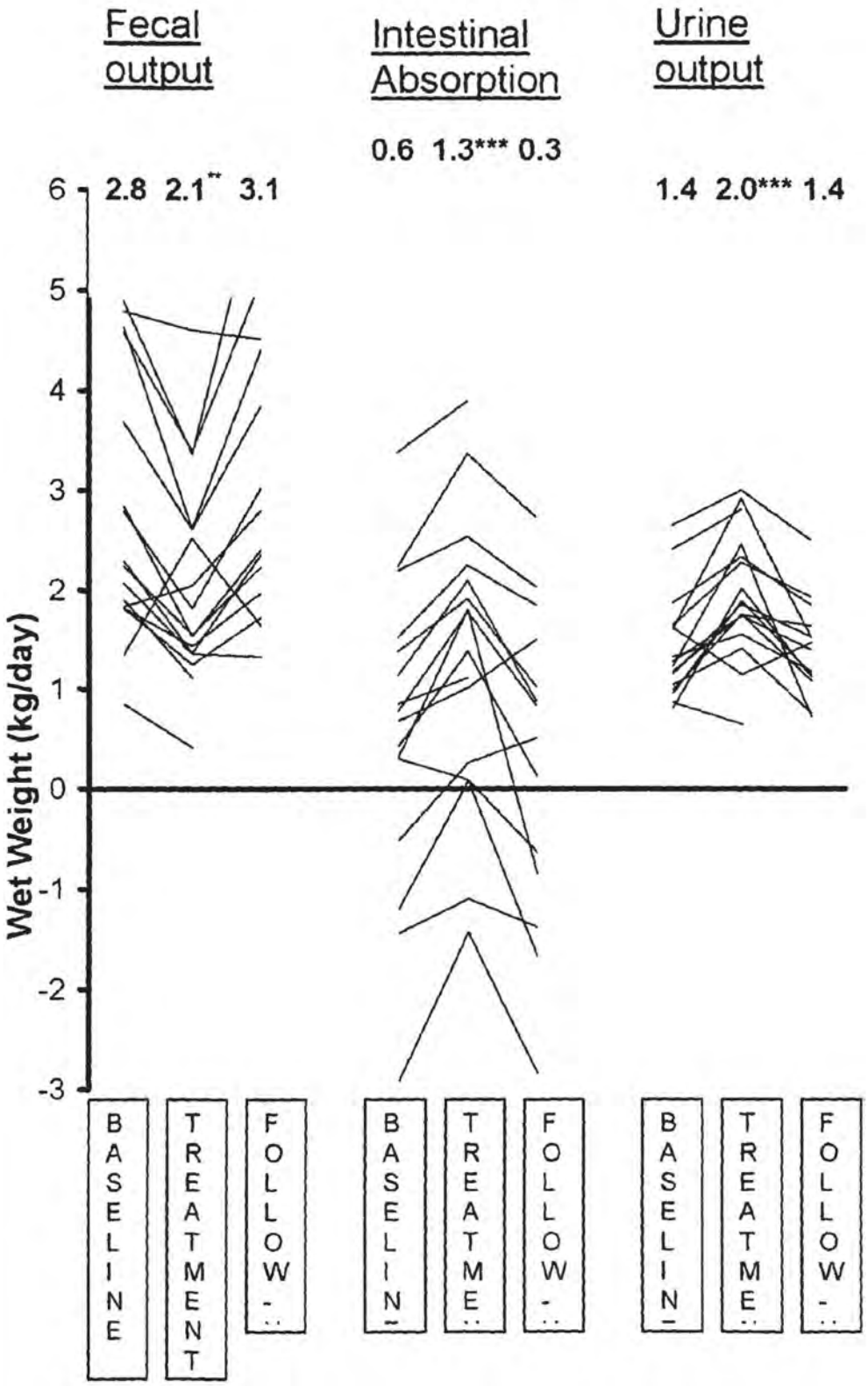

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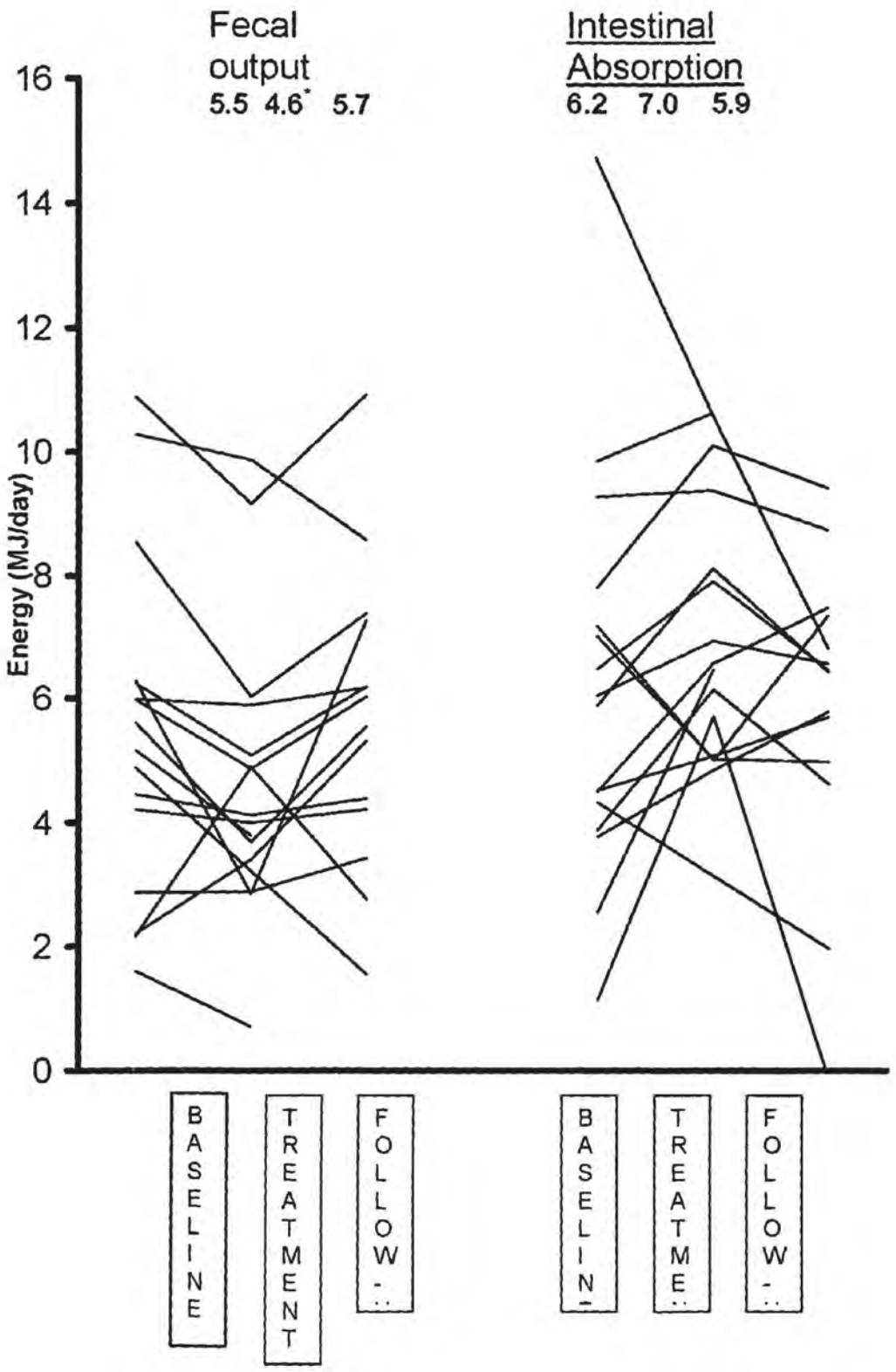
Figure 2.



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TREATMENT OF SHORT BOWEL SYNDROME PATIENTS WITH COLON-IN-CONTINUITY

FIELD OF THE INVENTION

This invention relates to products and methods useful medically to treat patients presenting with short bowel syndrome. More particularly, the invention relates to glucagon-like peptide 2 (GLP-2) and other GLP-2 receptor agonists effective to improve intestinal function particularly in patients presenting with short bowel syndrome with colon-in-continuity.

BACKGROUND TO THE INVENTION

The estimated prevalence of short bowel syndrome (SBS) patients with non-malignant disease requiring home parenteral nutrition (HPN) is at least 40 per million of the U.S. population. SBS usually results from surgical resection of some or most of the small intestine for conditions such as Crohn's disease, mesenteric infarction, volvulus, trauma, congenital anomalies, and multiple strictures due to adhesions or radiation. Surgical resection may also include resection of all or part of the colon. SBS patients suffer from malabsorption that may lead to malnutrition, dehydration and weight loss. Some patients can maintain their protein and energy balance through hyperphagia; more rarely they can sustain fluid and electrolyte requirements to become independent from parenteral fluid.

Although long-term parenteral nutrition (PN) is life saving in patients with intestinal failure, it is expensive, impairs quality of life and is associated with serious complications such as catheter sepsis, venous occlusions and liver failure. Treatments that amplify absolute intestinal absorption, and eliminate or minimize the need for PN have great potential significance to SBS patients.

The endogenous meal-stimulated hormone, glucagon-like peptide-2 (GLP-2), raises considerable interest for SBS patients. GLP-2 functions to slow gastric emptying, reduce gastric secretions, increase intestinal blood-flow and stimulate growth of the small and large intestine. In animal studies, GLP-2 administration induces mucosal epithelial proliferation in the stomach and small and large intestine by stimulation of crypt cell proliferation and inhibition of enterocyte apoptosis.

SBS patients with end-jejunostomy and no colon have low basal GLP-2 levels and limited meal-stimulated GLP-2 secretion due to removal of GLP-2 secreting L-cells, which are located primarily in the terminal ileum and colon. This GLP-2 deficiency results in a minimal adaptive response following resection and could explain the gastric hypersecretion, rapid intestinal transit and lack of intestinal adaptation observed in these SBS patients.

Jeppesen et al. (Gastroenterology 2001; 120:806-815) have described positive benefit in an open-label study using pharmacologic doses of native GLP-2 in SBS jejunostomy patients. There was significant improvement in intestinal wet weight absorption and a more modest improvement in energy absorption that led to an increase in body weight, lean body mass and a rise in urinary creatinine excretion.

In contrast, SBS patients with colon-in-continuity have elevated basal endogenous GLP-2 levels resulting in an adaptive response to resection characterized by improved wet weight gain and energy absorption. The potential for added

SUMMARY OF THE INVENTION

It has now been determined that intestinal absorption is enhanced in SBS patients presenting with colon-in-continuity when those patients are treated with a GLP-2 receptor agonist.

Thus, in one aspect, the present invention provides a method for enhancing intestinal absorption in a patient with short bowel syndrome, comprising the steps of selecting for treatment a short bowel syndrome patient presenting with at least about 25% colon in continuity with remnant small intestine, and treating said patient with a GLP-2 receptor agonist to enhance intestinal absorption by said patient.

In a related aspect, the present invention provides for the use of a GLP-2 receptor agonist in the preparation of a medicament for enhancing intestinal absorption in short bowel syndrome patients presenting with at least about 25% colon in continuity with remnant small intestine.

In a preferred embodiment, the GLP-2 receptor agonist is [Gly2]hGLP-2, known as teduglutide.

BRIEF REFERENCE TO THE DRAWINGS

Embodiments of the invention are now described with reference to the accompanying drawings in which:

FIG. **1** illustrates results measured in terms of fecal wet weight, intestinal wet weight absorption and urine weight in the individual patients at Baseline (Days −3 to 0), during treatment (Days 18 to 21), and at follow-up (Days 39 to 42).

FIG. **2** illustrates results measured in terms of fecal energy excretion and intestinal absorption in the individual patients at Baseline (Days −3 to 0), during treatment (Days 18 to 21), and at follow-up (Days 39 to 42).

DETAILED DESCRIPTION

The positive effect of GLP-2 receptor agonists on intestinal absorption in SBS patients that retain at least some, e.g., >25%, of their colon is particularly surprising. These patients have essentially retained GLP-2 producing tissue and, indeed, show elevated basal levels of the endogenous GLP-2 that can be as high as meal stimulated levels in normal, healthy individuals and that, in normal individual, is responsible for maintenance of the intestinal lining required for intestinal absorption. There is nevertheless significant clinical benefit for these patients, manifest principally as enhanced intestinal absorption as indicated by increased absolute wet weight absorption, when they are treated in accordance with the present method.

More particularly, patient candidates for the present treatment are those presenting with SBS resulting from small intestine resection which may be secondary to Crohn's disease, vascular ischemic disease, malrotation or volvulus, trauma, congenital anomalies, or multiple strictures due to adhesions or radiation and who require parenteral nutrition to meet their needs. As patients presenting with short bowel syndrome, such patients typically retain, following resection, a length of small intestine that is within the range from at least about 25 cm and at most about 200 cm., e.g., from about 50-150 cm. Such SBS patients include those patients presenting with jejunostomy, in which part of the jejunum is resected and generally all of the ileum, and/or ileostomy in which part of the ileum is resected and the jejunum may or may not be present. SBS patients with jejunostomy or ileostomy gener-

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SBS patients selected for treatment by the present method are those who retain, in continuity with remnant small intestine, at least some length of their colon, such as at least about 25%, and desirably 30%, 35%, 40%, 45% and preferably at least 50%, 60%, 70%, 80%, 90% or more. The remaining length of colon typically will be determined from the surgical records of a patient candidate. Expressed in other terms, preferred candidates for the present treatment are short bowel syndrome patients who retain colon sufficient to produce endogenous GLP-2 at levels that are at least greater than the negligible levels produced by patients with no colon, and ideally are similar to those GLP-2 levels produced by healthy volunteers. Endogenous GLP-2 levels for normal, healthy individuals are 15±2 pmol/L fasted, and 61±9 pmol/L fed. Candidates for the present treatment thus are SBS patients that retain sufficient functional colon to produce at least about 10%, 20%, 30%, 40%, 50% or more of such levels in the fed state, e.g., at least about 5 pmol/L fed, and desirably 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65 and 70 pmol/L endogenous GLP-2 in the fed state.

In a preferred embodiment, treatment candidates are those short bowel syndrome patients who retain at least 50% or more of colon length in continuity with remnant small intestine. Such a treatment candidate is identified herein as a patient with ≧50% colon-in-continuity. In other preferred embodiments, the SBS patient with colon in continuity has a remnant small intestine at least about 50 cm in length which, desirably but not essentially, incorporates at least a portion of the ileum.

The patients can be selected for treatment by the present method at any time following the surgical resection. That is, patients that are undergoing adaptation, as well as those who have had sufficient time to adapt following the surgery, are acceptable treatment candidates.

Treatment of short bowel syndrome patients presenting with colon-in-continuity, in accordance with the present method, is effective to enhance intestinal absorption, particularly of fluid including water and salts, but including nutrients as well. This effect is revealed particularly as a treatment-mediated, statistically significant increase in absolute wet weight absorption, which is determined by subtracting fecal wet weight from diet wet weight using a vigorous nutrient absorption test. The effect of treatment is also generally seen as a reduction in fecal wet weight, an increase in urine wet weight, a reduction in energy excretion (measured as herein described), and in other respects noted in the examples herein.

The present treatment method entails dosing the selected patient with a GLP-2 receptor agonist using a treatment regimen effective to enhance intestinal absorption. Such GLP-2 receptor agonists are characterized as molecules that bind with, preferably selectively, and stimulate the human GLP-2 receptor, as reported by Monroe et al. in U.S. Pat. No. 6,077,949 issued Jun. 20, 2000, incorporated herein by reference. Briefly, GLP-2 receptor agonists are revealed as agents that trigger production of, or trigger an elevation in the level of, a second messenger coupled to the human GLP-2 receptor, when exposed to a host cell that produces that receptor naturally or is transfected with DNA encoding that receptor.

In one embodiment of the invention, the GLP-2 receptor agonist is human GLP-2. In other embodiments, the GLP-2 receptor agonist is a vertebrate, e.g., mammalian, homolog of human GLP-2. Thus, GLP-2 receptor agonists useful in embodiments of the present invention include GLP-2 having the sequence found in GLP-2 endogenous to human, cow, pig,

In other embodiments, the GLP-2 receptor agonist is an analog of human GLP-2, which incorporates at least one, and usually not more than 5, e.g., 1, 2 or 3, amino acid substitutions or additions, and may also have a C-terminal truncation of from 1 to 5 or more amino acids.

In a preferred embodiment, the GLP-2 receptor agonist is a GLP-2 peptide analog that is altered to prolong serum half-life. In a particularly preferred embodiment, the GLP-2 peptide incorporates an amino acid substitution that renders the peptide resistant to the endogenous enzyme dipeptidyl peptidase IV (DPP-IV). Such analogs incorporate an appropriate substitution of the Ala2 residue desirably, but not essentially, by a genetically encoded amino acid, to permit recombinant production of the desired protein. Amino acids that can usefully substitute at Ala2 to provide GLP-2 analogs that retain GLP-2 receptor agonist activity and are less susceptible to DPP-IV include GLy, D-Ala, Val, Glu, Lys, Arg, Leu and Ile. Still other GLP-2 analogs include those substituted at Met10 by an amino acid that is less sensitive to oxidation.

In alternative embodiments, the GLP-2 peptide, or GLP-2 peptide analog is derivatized, for instance at an internal or substituted lysine, to prolong serum half-life by conjugation with lipophilic groups, with polyethylene glycol groups, with albumin or with any other functional group having the desired effect of reducing the rate at which the peptide is degraded endogenously following its administration. Such derivatized forms may be derivatized analogs of GLP-2, which carry substitutions, such as conserved or non-conserved lysine substitutions, having no appreciable negative effect on GLP-2 receptor activation but allowing for conjugation of the desired functional group. It will be appreciated that these derivatized forms of GLP-2 or of GLP-2 analogs are considered to be GLP-2 receptor agonists if they exert their endogenous effect through the GLP-2 receptor after administration, even if this GLP-2 receptor agonist property is not displayed while in the pro-drug, pre-administration form.

A wide variety of useful active GLP-2 analogs and derivatives have been described in the literature, as revealed in U.S. Pat. No. 5,789,379 issued Jun. 20, 2000 and related WO97/39031 published Oct. 23, 1997 which teach site-specific GLP-2 analogs; in WO02/066511 published Aug. 27, 2003 which teaches albumin-derivatized forms of GLP-2 and analogs, and in WO99/43361 published Oct. 14, 1999, WO04/035624 published Apr. 29, 2004 and WO04/085471 published Oct. 7, 2004 which describe lipophilic-derivatized forms of GLP-2 and analogs.

In a particularly preferred embodiment of the present invention, the GLP-2 receptor agonist is [Gly2]hGLP-2, known as teduglutide.

The dosing regimen effective to treat the SBS patients with colon-in-continuity entails delivering the selected GLP-2 receptor agonist to the patient for a time and at a dose sufficient to enhance intestinal absorption. As noted in the examples herein, and according to a preferred embodiment of the present invention, one suitable treatment regimen entails once daily administration of teduglutide, by subcutaneous injection in the abdomen, thigh or arm, at a dose in the range from 30 to 150 ug/kg/day for a period of about 21 days. It is anticipated that effective daily doses of teduglutide, as well as human GLP-2 per se and other GLP-2 receptor agonist with comparable properties, will lie generally in the broader range from about 5 to 500 ug/kg/day e.g., from 10 to 400 ug/kg/day, such as 20 to 300 ug/kg/day.

It will be appreciated from these results that a similarly beneficial effect can be expected when using either tedug-

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