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A safety and pharmacokinetic dosing study of glucagon-like peptide 2 in infants with intestinal failure☆

David L. Sigalet [a,*], Mary E. Brindle [a], Dana Boctor [b], Bryan Dicken [c], Viona Lam [a], Lily Sia Lu [a], Elaine de Heuvel [a], Bolette Hartmann [d], Jens J. Holst [d]

[a] Pediatric Surgery, Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada
[b] Pediatric Gastroenterology, Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada
[c] Pediatric Surgery, Stollery Children's Hospital/University of Alberta, Edmonton, AB, Canada
[d] NNF Center for Basic Metabolic Research, Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

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ABSTRACT

Background & Aims: Glucagon-like peptide 2 (GLP-2) analogues are approved for adults with intestinal failure (IF), but no studies have included infants. This study examined the pharmacokinetics (PK), safety, and nutritional effects of GLP-2 in infants with IF.
Methods: With parental consent (Health Canada Protocol:150,979), parenteral nutrition (PN)-dependent infants were treated with 5–20-μg/kg/day GLP-2 for 3 days (phase 1), and if tolerated continued for 42 days (phase 2). Nutritional therapy was by primary caregivers, and follow-up was to one year.
Results: Six patients were enrolled, age 5.4 ± 3.2 months, bowel length: 27 ± 12% of predicted, PN dependent (67 ± 18% of calories). GLP-2 did not affect vital signs, nor were there significant adverse events during the trial. Dosing 5 μg/kg/day gave GLP-2 levels of 52–57 pmol/L, with no change in half-life or endogenous GLP-2 levels. Enteral feeds, weight, Z scores, stooling frequency, and citrulline levels improved numerically. The trial was discontinued early because of a drop in potency.
Conclusions: GLP-2 was well tolerated in infants, and pK was similar to children with no changes in endogenous GLP-2 release. The findings suggest that GLP-2 ligands may be safely used in infants and may have beneficial effects on nutritional status. Further study is required.
Level of evidence: 2b Prospective Interventional Study.

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Intestinal failure (IF) because of nutrient malabsorption following intestinal resection and the subsequent requirement for prolonged parenteral nutrition (PN) is a common problem in neonates [1]. Worldwide, there is an increasing incidence of such babies, because of the increase in survival of premature infants, and the associated increased incidence of necrotizing enterocolitis (NEC); NEC is the most common cause of IF [1]. The provision of nutritional support (PN) and allowing time for the remaining intestine to heal and adapt are the fundamental therapies for this patient group [2,3]. The process of intestinal adaptation is a fundamental up-regulation of the nutrient absorptive capacity of the remnant intestine; this process occurs naturally only in response to enteral nutrient stimulation. However, in sick neonates, feeding is often delayed because of many factors. There are no standard pharmacologic therapies to improve the function of the residual intestine or hasten the course of healing or adaptation. The ability to pharmacologically stimulate intestinal adaptation would be a major advance in therapy for this patient population.

Glucagon-like peptide-2 (GLP-2 1–33) is an enteroendocrine hormone which is a key regulator of growth and function in the intestinal mucosa [4,5]. It is synthesized by the L-cells of the small intestine, which are most numerous in the terminal ileum. L-cells are situated on the basal aspect of the intestinal mucosa but project to the lumen to 'taste' the intestinal content [6]. They release GLP-2 (and GLP-1) in response to sensing undigested nutrients, especially free long chain fatty acids, in the intestine. In turn, GLP-2 activates a specific receptor, which is exclusively expressed on enteroendocrine cells, the enteric neuronal system and myofibroblasts of the intestine, but not on the epithelium directly [7]. Acutely GLP-2 slows motility, increases mesenteric blood flow and reduces enteric secretions; chronically it is trophic for the small intestinal mucosa [8–10]. In animals following intestinal resection, GLP-2 levels are strongly correlated with the amount of partially digested nutrients in the intestinal lumen; chronic elevations in GLP-2 levels stimulate an increase in intestinal surface area. This then increase absorption, and decreases the amount of residual nutrients in the lumen at the terminal ileal L-cell sensor location, and GLP-2 levels fall [9–12]. Thus GLP-2 can be thought of as a regulator in a feedback

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* Corresponding author at: Department of Surgery, Alberta Children's Hospital/University of Calgary, 2888 Shaganappi Trail NW, Calgary, AB T3B 6A8, Canada. Tel.: +1 403 955 2271; fax: +1 403 955 7634.
E-mail address: dsigalet@sidra.org (D.L. Sigalet).

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system or 'axis' controlling intestinal nutrient absorption, similar to the insulin–glucose axis.

In infants, this GLP-2 'axis' of nutrient-stimulated GLP-2 production in response to feeds is highly active. In fed premature infants, postprandial levels of GLP-2 are very high (up to 450 pM/L), but are low in fasted infants [13]. In infants with IF, serum GLP-2 concentrations correlate with residual small intestinal length, intestinal absorption and ultimately survival [13,14]. Thus, we hypothesized that exogenous GLP-2 therapy would improve intestinal function in this population. However, there are no studies examining the safety, metabolism, or physiologic effects of GLP-2 in infants.

The present study was planned as a phase I–II trial with the primary aim of examining the safety and pharmacokinetics of native glucagon-like peptide-2 (GLP-2) (1–33) in infants with anatomic short bowel syndrome or intestinal failure. Because this is the first study in human infants, we began with a low dose of 5 μg/kg, and planned to use higher doses once the preliminary safety study was completed. The dosing was based on a safety study using 40 μg/kg/day in neonatal piglets, supported from day 2 of life through to weaning and on to day 44, which showed that PK and metabolism in these neonatal animals was similar to that seen in adult humans [15]. Additional support for the safety in pediatric patients was provided by our recent positive experience using a dose of GLP-2 at 20 μg/kg/day in children with IF [16]. The secondary aim of the study was to obtain preliminary data to determine the nutritional effects of GLP-2 therapy, to guide future investigations in infants.

1. Methods

With institutional ethic board approval (Clin trials # NCT01573286, Health Canada Reference GLP-2-01 150,979, University of Calgary Conjoint Health Ethics Board #21691), families of infants who, on the basis of residual intestinal length had anatomic short bowel syndrome (SBS) or had demonstrated IF on the basis of not weaning from PN, were approached to participate in the study. Patients were less than one year corrected age at the start of therapy, with SBS/IF post-surgery (resection or repair of gastroschisis). Short bowel syndrome was defined as a total remaining small intestine less than 40% of predicted for gestational age, based on the expected length as published by Strujis et al. [17]. Intestinal failure was defined as a requirement for >50% of calories by PN more than 45 days from the last intestinal surgery [1,3]. The exclusion criteria were related to co-morbidities (either systemic diseases or intestinal mucosal) which would interfere with the potential for the recovery of normal intestinal function (Table 1).

1.1. Subjects

Subjects were primarily inpatient post-surgical patients who had been transitioned from the NICU to the pediatric ward for care following a resection. During the trial they were treated following the standard nutritional care protocol of the institution's intestinal rehabilitation team. Patients were enrolled at 2 sites, following a common treatment protocol. After the study, patients were cared for by the IF care team, with clinic visits for study specific review at 1, 6 and 12 months post therapy. At enrollment, demographics and anatomic data were extracted from the chart, including operative measurements of bowel length, and nutritional parameters of weight, weight gain, tolerance of enteral formula and stool output. Bowel length was expressed as both the absolute length as measured in the operating room, and as a percentage of the expected small intestinal length, based on the weight of the child [17]. Lab parameters followed were routine PN blood work (complete blood counts, electrolytes, creatinine, urea, AST, ALT, bilirubin, gamma GT, protein and albumin levels). Twice weekly, nutritional parameters and an overview of the general clinical status of the infant was obtained. Clinical status evaluation was primarily for episodes of sepsis, any unusual swelling or edema, or other potential adverse events.

During the study there were no study mandated changes in nutritional support of the patients. Advancement of feeds and tapering of PN were done by the primary care team, independent of the study. Similarly, the use of other medications, including the use of antibiotics and motility enhancing agents was at the discretion of the primary care team.

1.2. Study design

A quasi-experimental interrupted time series design with patients from a convenience sample was used. The therapeutic agent, native human glucagon-like peptide 2 (1–33), was produced as a lyophilized powder by solid state synthesis (CS Bio, Menlo Park CA) (>98% purity) and prepared as a sterile solution in alkalinized saline (0.9% NaCl alkalinized to pH 8.5–9.5 by addition of 0.05 M NaOH). Powdered GLP-2 was dissolved in individual vials (1.5 mg in 1.5 ml) following good manufacturing practices (GMP) by the experimental therapeutics program of the British Columbia Cancer Agency, Vancouver BC (Lot IC115, May 2009). The peptide was stored as a frozen solution at −20 °C until used. Stability was demonstrated by repeated testing using an identical mixing and freezing sequence, using mass spectroscopy at 6 month intervals following manufacture, with minimal loss of potency (>90% of nominal peptide concentration) until July 2014. (Testing done by Maxam Corporation, Burnaby BC, following GMP standards.)

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients less than 1 year of age (corrected gestational age) AND	Significant extra-intestinal disease (e.g. grade IV intraventricular hemorrhage, severe hypoxic encephalopathy)
Anatomic SBS, with less than 40% of expected bowel length (for gestational age) and a requirement for >50% of calories by PN, more than 45 days from last intestinal surgery OR	Significant cardiovascular, hemodynamic or respiratory instability as noted by 1) requirement for dopamine >4 mcg/kg/min, 2) high frequency ventilatory support, 3)extracorporeal membrane oxygenation
Intestinal Failure with a requirement for >50% of calories by PN, more than 45 days from an intestinal resection, independent of the length of remnant small intestine OR	
Gastroschisis with a requirement for >50% of calories by PN, and more than 45 days from last abdominal/intestinal surgery	Hepatic disease defined as direct bilirubin >100 μmol/L (5.2 mg/dL)
	Renal disease defined as BUN >80 or creatinine >90 μmol/L (1.5 mg/dL)
	Inborn errors of metabolism necessitating protein restriction or other special diet
	Ongoing sepsis syndrome, as noted by refractory hypotension, thrombocytopenia, acidosis, and/or bacteremia
	Primary motility defect such as intestinal pseudo-obstruction
	Absorptive defects (such as microvillus inclusion disease)
	Coagulopathy which precludes the use of subcutaneous injections
	Allergy to GLP-2 or any of the constituents of the GLP-2 IC-115 preparation

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