



Case report

Effect of teduglutide on restoring oral autonomy for magnesium in two patients with short bowel

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ABSTRACT

It is not known whether Teduglutide can allow patients with Short bowel syndrome, previously dependent on continuous or periodic intravenous (IV) magnesium, to attain oral autonomy with or without supplementation. Here, we report on two patients previously dependent on continuous or intermittently administered IV magnesium to achieve autonomy from IV, one with and one without oral supplementation that was previously ineffective in both patients.

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Introduction

Patients with short bowel syndrome (SBS) with a jejunostomy rarely maintain normal or near normal levels of magnesium with an oral diet, supplements, or a combination of the two. These patients usually need daily or periodic intravenous (IV) supplementation of magnesium to avoid clinical manifestations of deficiency. Maintaining serum magnesium above the recommended lower limit of 0.7 mmol/L is important for avoiding complications such as muscle spasms and tetany with associated positive Trousseau's and Chvostek's signs [1].

Teduglutide is a receptor agonist on glucagonlike peptide (GLP)-2 receptors in the intestine, which promotes absorptive capacity by proliferation of microvilli [2]. This has conferred the indication of this drug as a treatment for SBS because it makes it possible for patients with reduced surface area to functionally compensate by absorbing more fluid and calories and thus safely reduces frequency of IV infusions with potential translation into a reduction of serious complications of long-term IV therapy of a metabolic and vascular nature.

Although teduglutide has been shown to result in oral autonomy from IV fluid and protein–calorie infusions, it has not been demonstrated to allow autonomy from IV magnesium, and one study raised questions as to whether it is possible for magnesium

[2]. We present the details of two patients previously dependent on continuous or periodic IV magnesium to become autonomous with or without oral supplements.

Patient

The first patient was a 62-y-old woman with quiescent Crohn's disease. Her recent surgical history and gut anatomy included pancolectomy in the second decade of life with one revision of an end ileostomy with resection of a persistent fistula culminating in a 150-cm small bowel remnant as an end jejunostomy. Clinical course is represented in Figure 1 (there were no confounding medical conditions or medications interfering with magnesium balance). The patient's Crohn's disease was quiescent with sulfasalazine treatment.

Attempts were made in this patient to maximize oral absorption of magnesium by using large molecular-weight organic compounds of magnesium (including both magnesium glucoheptonate and magnesium pidolate or a combination of both; Fig. 1) formulated to be isotonic and slowly infused through a nasogastric tube. The patient knew how to self-insert a nasogastric tube at home and declined more permanent enteral access. Despite this complex arrangement to which adherence was very good, the combination of nasogastric and the oral route only maintained a level of between 0.56 and 0.58 mmol/L serum magnesium, albeit asymptomatic. After introduction of teduglutide, the levels rose to 0.7 mmol/L without supplement (Fig. 3).

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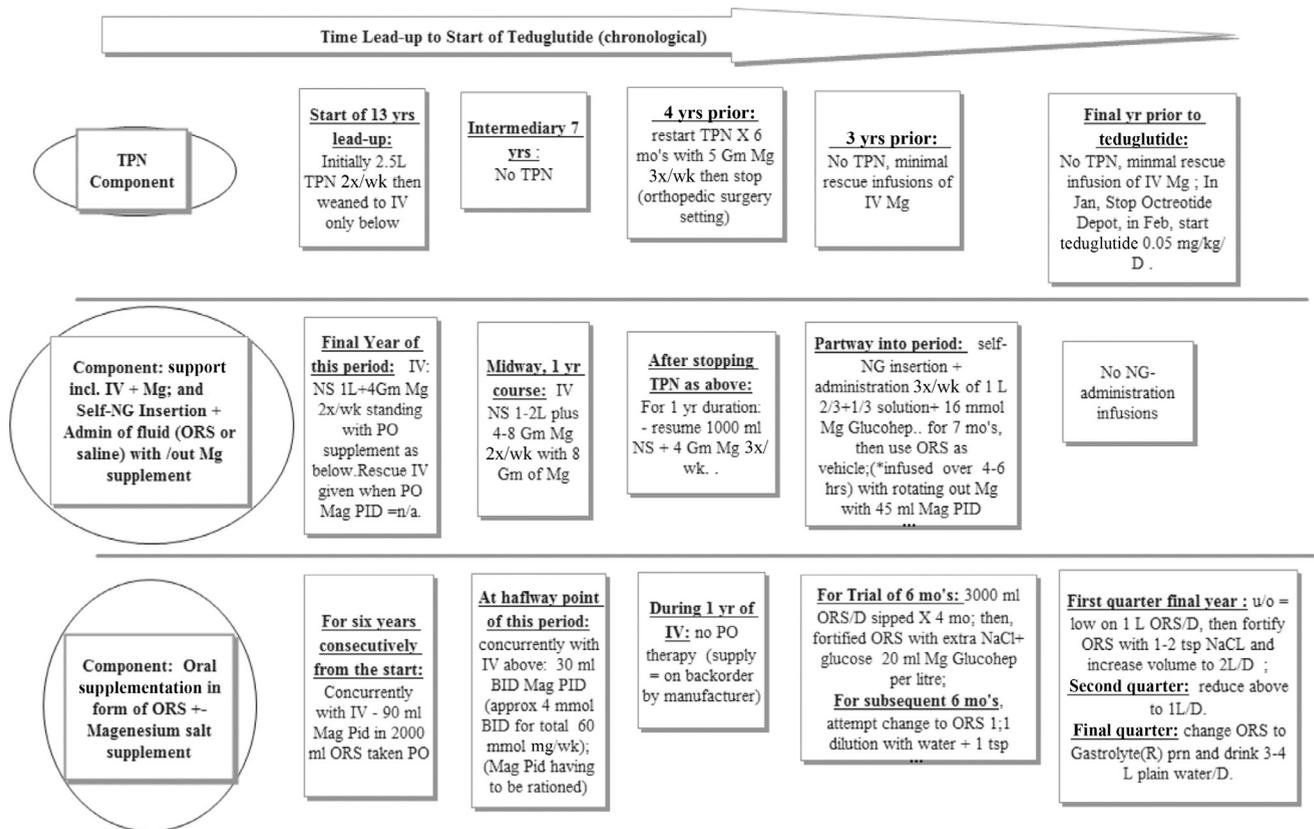


Fig. 1. Patient 1 clinical course and timeline. Gastrolyte®, commercialized ORS; ORS, oral rehydration solution; Mag PID, magnesium pidolate; MgGlucohep, magnesium glucoheptonate; n/a, not available because of back-order or supply out of stock; NG, nasogastric; NaCl, salt; TPN, total parenteral nutrition; u/o, urine output.

Patient 2

Patient 2 was a 70 y old woman with quiescent Crohn's disease. Her recent surgical history and gut anatomy included a colectomy and ileostomy in the fourth decade of life and a decade later, a revision of ileostomy, which led to total parenteral nutrition. Clinical course is represented in Figure 2 and includes recent weights (no confounding medical conditions or medications interfering with magnesium balance). The patient's Crohn's disease was kept quiescent with azathioprine. The patient's stoma generated voluminous outputs immediately after meals. Subsequent to switching from IV administration to the poorly bioavailable oral supplement, her serum magnesium was at an all-time low of 0.58 mmol/L (not unlike her prior 0.6 mmol); however, despite uncertainties of oral absorption, the ensuing levels only went upward and this effect was so sustained that it would appear to suggest that teduglutide administration was gaining traction with its effect becoming amplified despite management being undermined with uncertainties of oral administration of magnesium. Serum magnesium rose to 0.67 mmol/L and then to 0.7 mmol/L with the same constant dose of oral supplement (Fig. 4). Subsequent serum values after the last plotted value were not available for the next 6 mo because the patient seasonally relocates south during winter and is outside of a health care system. The patient remained asymptomatic of any signs of hypomagnesemia throughout and required no rescue IV magnesium. When she returned 6 mo later, her magnesium was 0.68 mmol/L, which reflected some changes in oral magnesium brand the patient had resorted to while temporarily relocated.

Discussion

Patient 1 shows the effect of maximizing absorption of magnesium from oral supplement by using a large molecular-weight magnesium organic compound likely to have a relatively low osmolality and by slowly infusing this supplement to allow time for absorption. Despite these measures, including formulating the preparation in components of oral rehydration solution to be overall isotonic, we only succeeded in maintaining a precarious level of serum magnesium of 0.57 mmol/L. After the use of teduglutide, the levels normalized without supplement and seemingly the teduglutide sustained this steady state shortly into the wake of a period where it could not have been remotely imagined that the patient could get by with only the magnesium her oral diet accorded her much less recover from her profoundly low values without IV magnesium. In patient 2, once IV magnesium was discontinued, the already-low baseline serum magnesium level of 0.56 mmol/L gradually rose upward in the window of time for the onset of effect of the drug as reported in the literature. Given time on teduglutide, it steadily rose to 0.7 mmol/L after 25 wk into treatment. This patient, of note, presented with a confounding serum magnesium during regular IV, having dropped below her baseline, suggesting any one or more of the following effects either from oral dietary discretions driving up the volume of stoma outputs containing magnesium and/or different timings in visits to the lab and/or subclinical inflammation promoting magnesium secretion in the stoma output.

The overall pattern of the patient's dependency on IV support is, in a manner, in parallel with other observations that absorption increases with duration of administration, with clinically meaningful reductions in dependency on IV carbohydrate calories and water in a

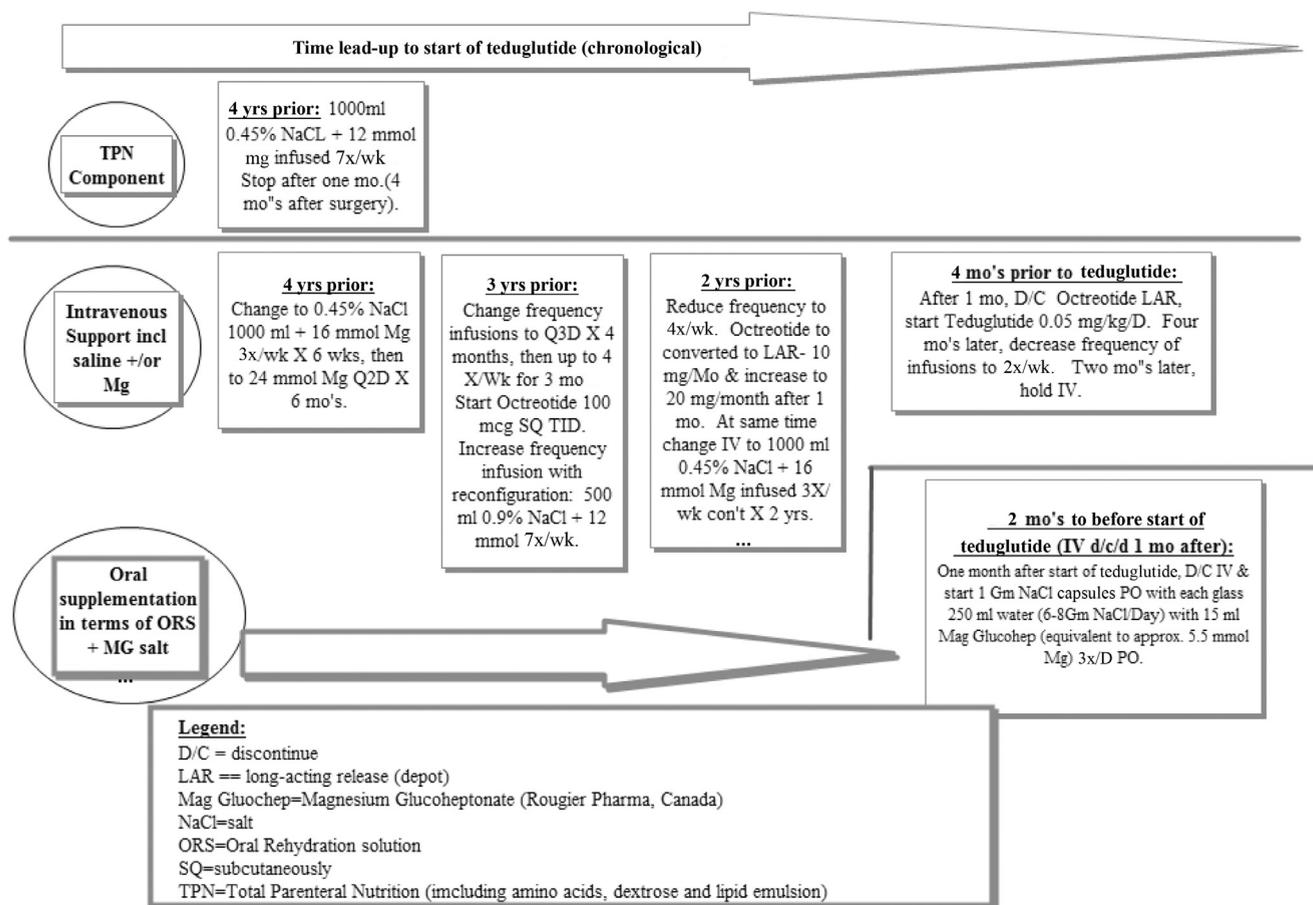


Fig. 2. Patient 2: 16-month period with 10-month lead-up to teduglutide, including stopping of nasoenteral delivery therapy and follow-up.

progressive, yet highly intravariability manner that spans from 20 to 30 wk [3]. Citrulline marker absorption was shown to increase, however, investigations looking at any other specific nutrient or molecule and delineating the effect of teduglutide on modulating motility time, are lacking in the literature [3]. Both patients displayed positive response to the drug after a lead time to onset of action, which is consistent with the literature [3]. Differences in the respective times of onset and the rapidity of escalating effect of the drug between the patients may be due to differences in contributing trophic effects from the composition of their different diets including dietary fiber, quality of the diseased intestine remaining given their varying durations of inflammation of Crohn's disease, their difference in age, and finally, intravariability pharmacogenetic factors not yet elucidated with this drug. It is a provocative hypothesis that both patients could drop their serum magnesium below their customary baseline values while on IV magnesium therapy. However, because only patient 1's level dropped after the teduglutide had its expected onset of action, it cannot be discounted that magnesium in the lumen of the intestine may in itself be a potential trophic factor promoting its own absorption over time in concert with teduglutide. An extension of that hypothesis would be that more magnesium in the form of supplement results in a steeper trajectory of increase in serum magnesium which in fact what is patient 2 demonstrated.

These patients illustrate that maintaining magnesium balance on oral supplements alone in the jejunostomy patient is problematic. Furthermore, many patients will not tolerate oral preparations. Even patients with SBS who are net absorbers will secrete water into the intestinal lumen while getting osmotically active oral magnesium. Patients are liable to develop

clinical instability, thus the oral regimen requires considerable adherence and a reliable access to magnesium pidolate, unlike our patient, who was periodically switched during manufacturer back-order situations. Most inorganic salts of magnesium are poorly soluble in the lumen of the intestine. Only a few soluble organic salts have clinical application, although some, such as magnesium citrate, are cathartic and licensed as preparations for endoscopy procedures. The added layer of uncertainty regarding reliable access to product when managing these patients is an additional reason for having started teduglutide administration, with the goal to maintain clinical stability when changing magnesium products. Of note, teduglutide is contraindicated in patients with a history of or at risk for gastrointestinal polyps or tumors and should not be initiated before screening and taking the time for clinical workup.

The first preteduglutide patient required 45 to 60 mmol/wk of magnesium to be administered enterally and spread out on top of any magnesium absorbed from her otherwise hyperphagic diet. Ladefoged et al. showed that absorption of magnesium in patients with SBS is reduced; however, the extent of malabsorption does not correlate to length of bowel [4]. In the intact, healthy small bowel, the absorptive capacity of a 300-cm segment was determined to be 2 mmol/h (48 mmol/d) [5]. The first patient had half this amount of bowel in the form of jejunum only. Confounding factors, in addition to presence of disease, include rapid transit time, modulation of transit time by the jejunal brake, and possibly, relative amounts present of dietary fibers modulating absorption in the small bowel [6,7]. In one study, the transit time in healthy volunteers for a magnesium

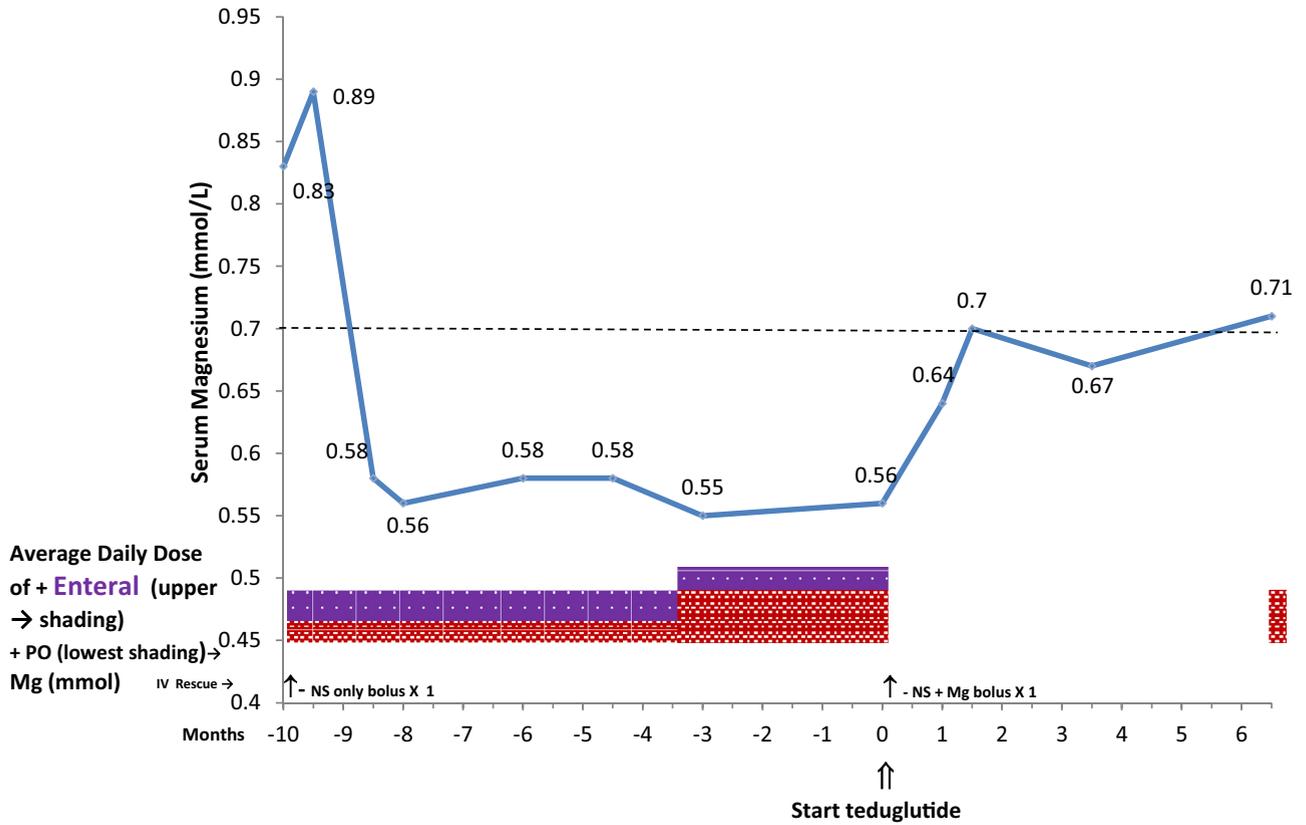


Fig. 3. Patient 1 clinical course and timeline. D/C, discontinue; LAR, long-acting release; Mag Glucohep, magnesium glucoheptonate; NaCl, salt, ORS, oral rehydration solution; SQ, subcutaneously; TPN, total parenteral nutrition.

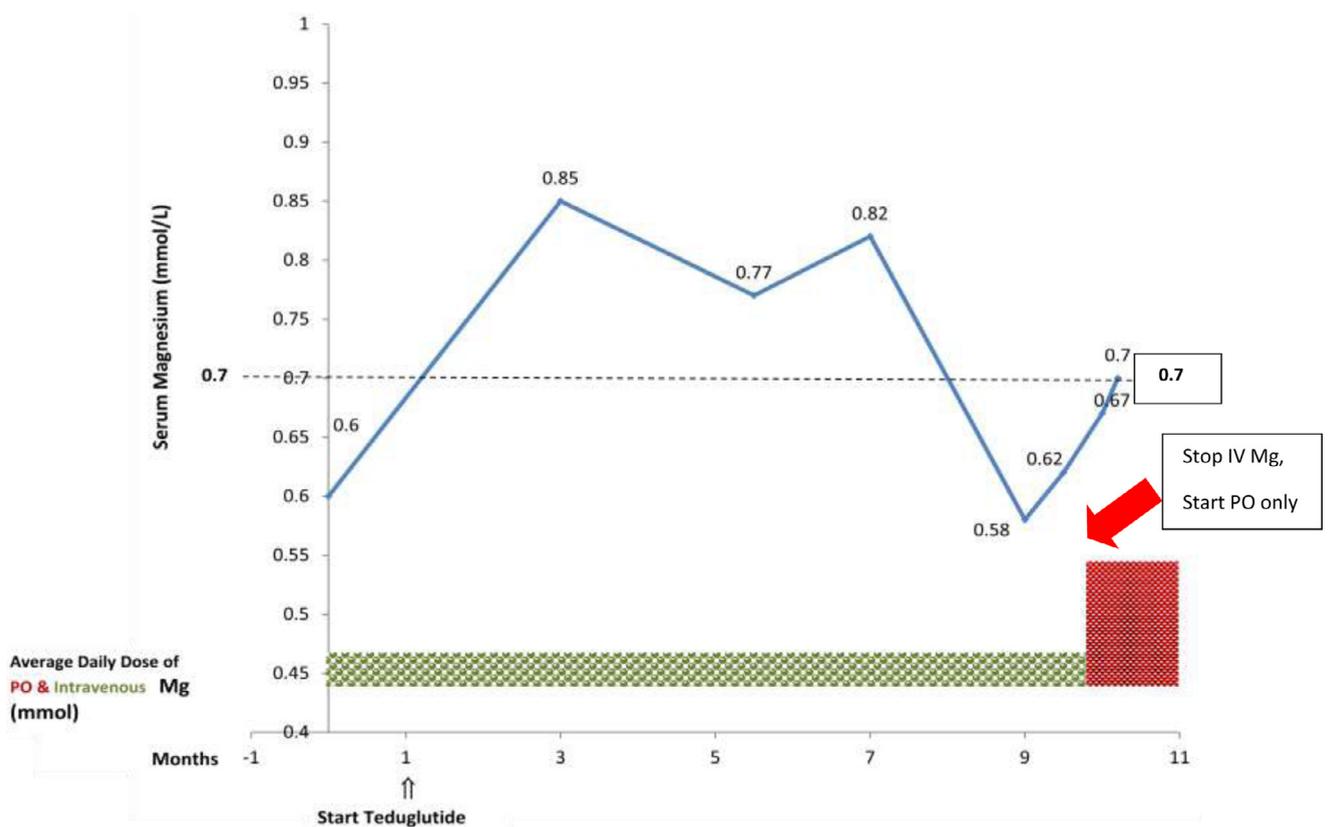


Fig. 4. Patient 2: 11-month period including 1 month lead-up to initiation of teduglutide, stopping IV therapy, and follow-up.

supplement from mouth to cecum was found to be 4 h [8]. Patients with short bowel would have an exponentially accelerated time, which is not linearly proportional to the length of bowel they have.

Conclusion

Teduglutide promoted magnesium homeostasis and obviated the need for IV administration, slow-administration technique, an organic salt form of magnesium, and the need for frequently monitoring magnesium levels. At no point were patients' safety compromised. Further studies are required to verify that this effect is sustainable in the long term.

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