

SCIENTIFIC LETTERS

Polyols: Is their use safe in enteral nutrition?



Poliolos: ¿es seguro su uso en nutrición enteral?

Enteral nutrition (EN) constitutes a way to provide nutritional support to patients who are not able to meet their nutritional requirements. However, it is not exempt of complications such as gastrointestinal symptoms (GI) or diarrhea. Although is widely accepted EN can cause diarrhea, there is little evidence to support it.¹ Formula composition has been postulated as a possible triggering factor, blaming FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) due to their osmotic effect. Maltitol, as polyol molecule, given in a high-enough dose would induce laxative effect. Following, we describe a case of possible diarrhea secondary to use of an EN formula maltitol-enriched.

In January of 2018, an 83-year-old woman with the relevant medical history of type 2 diabetes mellitus, hypertension, dyslipidemia, penicillin allergy and dependent for the activities of daily living after suffering a stroke in the past, was brought by her daughter to the Accident and Emergency Department. On admission, patient had swallowing difficulties, disability to eat and drink, right face drooping and speech difficulty. Her regular medicines were: Captopril 50 mg one tablet once a day (OD), Dipotassium Chlorazepate 10 mg one capsule OD, Furosemide 40 mg one tablet OD, Metformin 850 mg one tablet OD, Nimodipine 30 mg one tablet twice a day.

Patient was diagnosed of ischemic stroke (21st January), which was confirmed by brain scan. She was admitted in Internal Medicine Department. Aspirin 100 mg OD, Atorvastatin 80 mg OD, Candesartan 16 mg OD, Enoxaparin 40 mg OD and Omeprazole 40 mg OD were added to her regular medicines. Next day (22nd January) patient had temperature (38 °C) starting empirical treatment with Levofloxacin 500 mg OD 7 days course for possible respiratory infection. Levofloxacin and Omeprazole were stopped after 7 and 8 days of treatment respectively (28th January). There were not changes on the rest of her regular medicines during this admission, and after 13 days patient was discharged (2nd February).

Despite patient had a positive evolution on this episode, she had severe dysphagia from admission date, which did not improve, requiring texturized food and thickened

fluids in the beginning. After 2 days (23rd January), EN via nasogastric tube was started due to patient did not tolerate oral diet. Diabetic EN (Diason Energy HP[®], Nutricia Advanced Medical Nutrition[®]) 500 mL divided in 5 shots per day was prescribed, increasing 250 mL daily up to a maximum of 1000 mL daily divided into five doses. EN was well tolerated. After five days (28th January), this diet was changed to Glucerna Select[®] (Abbot Nutrition[®]) 1000 mL in 24 h, divided in 5 shots because Diason Energy or similar EN was not available due to manufacturing problems. At 28th January, patient presented gastrointestinal disorders (abdominal pain, flatulence and watery diarrhea). Nausea or vomiting was not reported.

After two days (30th January) having those gastrointestinal problems the physician contacted pharmacy to monitor her EN. Patient was assessed and reviewed by pharmacy team (Nutrition Support Specialist Pharmacists). Also an interview with the patient's relatives and nurses was conducted to check the correct administration technique (no changes on administration technique were reported and it was correct). In addition, patient's relatives denied any food allergy, intolerance, digestive disorders or gastrointestinal disease.

Nutritional requirements were calculated for the patient, estimating 1591 kcal per day² (80 kg, 160 cm, Body Mass Index: 31.25 kg/m²), however due to her obesity, pharmacy team agreed a low-calorie and high-protein nutrition (1000 kcal per day and 80–96 g protein) would be appropriated. Thereby, EN was changed to Diben Estandar[®], Fresenius Kabi 1000 mL over 24 h divided in 5 doses initially. Administration technique change to continuous feeding was discarded due to high suspicion that the EN formula was the cause of GI disorders and patient's family preferences. Next day (31st January), diarrheic stools ceased and rest of gastrointestinal symptoms. Patient continued with same EN for three more days until discharge from the hospital with good tolerance and follow up with Nutrition Support Unit to optimize patient's EN.

Diarrhea is one of the most common complications associated with EN. There are multiple contribute factors involved on its pathogenesis, such medication, infection, underlying disease and enteral nutrition.¹

Drugs have been reported as major cause of loose stools in hospitalized patient with enteral nutrition.³ In our patient, medication was reviewed as a possible cause. Omeprazole and Levofloxacin have been reported as cause of diarrhea, however both medicines were stopped (28th January) and GI episode continues. Thereby, it seems related

Table 1 Composition of different enteral nutrition formulas given during patient's admission.

Composition (per 500 mL)	Diason Energy HP [®]	Glucerna Select [®]	Diben Estandar [®]
Type of enteral nutrition	Diabetes HP/HC	Diabetes HP	Diabetes HP
Duration from admission day	Day 2 to Day 6	Day 7 to Day 9	Day 10 to discharge
Osmolarity (mOsm/L)	395	378	345
Lactose/gluten (g)	FREE	FREE	FREE
Fructose (g)	0	9.81	11
Fiber total (g)	7.5	7.2	7.5
Fiber % (soluble/insoluble)	80/20	43.17/56.83	74/26
Maltitol (g)	FREE	9.5	FREE
Tolerance	Good	Gastrointestinal symptoms/diarrhea	Good

HC: high calorie nutrition; HP: high protein nutrition.

with the enteral formula change, in regards of the start and stop diarrhea timeline.

Enteral nutrition also has been blamed as a cause of diarrhea. Enteral formula has been suggested as a contributing factor to (GI) symptoms. Three different EN formulas with different composition were prescribed during patient's admission (Table 1).

Patient developed diarrhea after starts Glucerna Select[®] EN and it stops after changing to Diben Estandar[®]. As stated in Table 1, the main difference between Glucerna Select[®] formula and the rest of EN formulas was its Maltitol content, which was 19 g per day (1000 mL) its intake. Maltitol is a slow absorption disaccharide polyol with a good glycaemic profile, being hypocaloric (2.1 kcal/g) and non-cariogenic molecule. In the healthy population cases of mild laxative effect and flatulence have been reported with daily amounts of 30–40 g.^{4,5} In addition, there are evidence that suggest the link between EN-associated diarrhea and polyols, such maltitol.^{6,7} In our case, GI symptoms appeared and gone suddenly, so it seems that a boosted mechanism could explain it. As known, Maltitol is absorbed around 40%, previous hydrolysis by the intestinal brush-border disaccharidases, to glucose and sorbitol.⁸ The unabsorbed amount (60%) is fermented through the intestinal flora. The Sorbitol that is a product of the hydrolysis of Maltitol, is absorbed only 25% and the rest, like the Maltitol, is fermented through the intestinal flora.⁷ Both Maltitol and Sorbitol are osmotic molecules that can lead in GI symptoms.^{6,7} As previously mentioned, patient was treated before start with Glucerna Select[®] EN with Levofloxacin without any GI disturbances. A marked reduction in commensal microbiota has been reported after a course of broad-spectrum antibiotic.² In our case, treatment with Levofloxacin could have altered gastrointestinal microbiota, decreasing Maltitol fermentation. A prolonged stay of this polyol at gastrointestinal level could have increased the osmotic charge. This fact would explain patient's abdominal discomfort and diarrhea. In addition, less soluble fiber proportion of Glucerna Select[®] could contribute with the mechanism suggested.

The Naranjo algorithm indicated that Maltitol content in Glucerna Select[®] was the possible cause of the patient's diarrhea.⁹

Low dose of Maltitol could be beneficial as additive for the EN, due to its glycemic profile and its low caloric content. However, in some circumstances, in which the gastrointestinal function is compromised, could be harmful leading on side effects (GI symptoms and diarrhea). Thus a deep patient's assessment and EN formula choice could be a key factor to avoid EN related problems.

References

- Chang SJ, Huang HH. Diarrhea in enterally fed patients: blame the diet? *Curr Opin Clin Nutr Metab Care*. 2013;16:588–94, <http://dx.doi.org/10.1097/MCO.0b013e328363bcdf>
- Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr*. 1990;51:241–7.
- Polage CR1, Solnick JV, Cohen SH. Nosocomial diarrhea: evaluation and treatment of causes other than *Clostridium difficile*. *Clin Infect Dis*. 2012;55:982–9, <http://dx.doi.org/10.1093/cid/cis551> [Epub ahead of print].
- Oku T, Hongo R, Nakamura S. Suppressive effect of cellulose on osmotic diarrhea caused by maltitol in healthy female subjects. *J Nutr Sci Vitaminol (Tokyo)*. 2008;54:309–14.
- Respondek F, Hilpipre C, Chauveau P, Cazaubiel M, Gendre D, Maudet C, et al. Digestive tolerance and postprandial glycaemic and insulinaemic responses after consumption of dairy desserts containing maltitol and fructo-oligosaccharides in adults. *Eur J Clin Nutr*. 2014;68:575–80, <http://dx.doi.org/10.1038/ejcn.2014.30>
- Halmos EP, Muir JG, Barrett JS, Deng M, Shepherd SJ, Gibson PR. Diarrhoea during enteral nutrition is predicted by the poorly absorbed short-chain carbohydrate (FODMAP) content of the formula. *Aliment Pharmacol Ther*. 2010;32:925–33, <http://dx.doi.org/10.1111/j.1365-2036.2010.04416.x>
- Halmos EP. Role of FODMAP content in enteral nutrition-associated diarrhea. *J Gastroenterol Hepatol*. 2013;28 Suppl. 4:25–8, <http://dx.doi.org/10.1111/jgh.12272>
- Livesey G. Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. *Nutr Res Rev*. 2003;16:163–91, <http://dx.doi.org/10.1079/NRR200371>
- Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–45.

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Can the molecular typing of the specific adenohypophyseal hormone genes be useful in the management of pituitary neuroendocrine tumours?



¿Puede ser útil la tipificación molecular de los genes específicos de las hormonas adenohipofisarias en el manejo de los tumores neuroendocrinos hipofisarios?

Dear Editor,

The accurate typification of the different Pituitary Neuroendocrine Tumours (PitNETs) is essential to their proper management and follow-up. The classification of PitNETs has evolved over time depending on advances in pathological techniques, ranging from the cellular staining properties to the immunohistochemical (IHC) and ultrastructural criteria of the tumour cells. The 2004 World Health Organization (WHO) classification of Tumours of the Pituitary Gland¹ was based on IHC techniques. However, while there is good concordance between clinical and IHC diagnosis in Functioning PitNETs, the information provided by IHC is not as accurate in Non-functioning PitNETs, mainly attributed to the absence of protein secretion by tumour cells (Null Cell Tumours) or to the secretion of proteins coming from different cell lineage types (Plurihormonal Tumours). That is why the recently published 2017 WHO classification of Tumours of the Pituitary Gland^{2,3} considers the study of the adenohypophyseal cell lineages as the pivotal aspect to classify the PitNETs. This concept is based on the IHC identification of the main transcription factors involved in the cellular differentiation of the adenohypophysis, mainly Pit-1, T-Pit and ESR-1.

However, the immunohistochemistry is a semi-quantitative technique that depends largely on the antibodies chosen and the observer. Indeed, we have recently observed an important variability in the IHC results between four different centres analysing two large series of PitNETs.^{4,5} In addition, in the Lyon's pathological series, using more sensitive IHC techniques, the percentage of Null Cell adenomas were reduced from 10% in 1992 to 1% in 2012.⁶ Moreover, the well-differentiated pituitary tumours mimic the normal anterior pituitary cells.⁷ Therefore, it is

essential to be sure that the analyzed tissue corresponds to the tumour specimen and not to the normal pituitary gland. As pituitary tumours are small, the amount of tissue given by the surgeon to the pathologist is usually scarce, and this can make the pathological studies difficult.

Unlike the 2017 WHO classification of Tumours of the Pituitary Gland, the 2016 Classification of Tumours of the Central Nervous System³ incorporated molecular and genetic patterns in the diagnosis of gliomas, medulloblastomas and other embryonal tumours. Accordingly, we published the complementary role of the molecular typing of pituitary-specific hormone genes to the IHC identification of PitNETs.^{4,5} However, its clinical applicability has not been established.

We have recently had the opportunity to study a 37-year-old man who came in our surgery because of sexual dysfunction and moderately high levels of Prolactin (PRL) (serial determinations of PRL of 58, 59 and 62 ng/mL; nv 4–21) with low levels of Total Testosterone (TT) (2 ng/mL; nv 3.12–10) and Gonadotropins (LH 2.1 U/L (nv 2–11.2) and FSH 3.6 U/L (nv 1–8)). The rest of pituitary function was preserved. The Magnetic Resonance Image revealed a 12 × 9 mm nodule on the left side of the gland, without extrasellar extension or displacement of the pituitary stalk. The nodule was hypointense in T1 and hyperintense in T2, suggesting a cystic component. Because of the uncertainty of the clinical diagnosis, our Neurosurgical team performed an Endoscopic Endonasal Surgery with complete resection of the tumour, disappearance of the sexual dysfunction and normalization of the hormone levels (PRL 2.7 ng/mL; TT 4.6 ng/mL, LH 3.7 U/L and FSH 5.7 U/L). The tissue sent for anatomopathological study consisted of adenohypophyseal fragments. The study with techniques for reticulin fibres as well as the IHC evaluation confirmed normal adenohypophyseal tissue without tumour component. Therefore, it was not possible to identify the subtype of PitNET, conditioning the follow-up of the patient in case of relapse of the tumour. The molecular study was carried out by Real-Time Quantitative PCR (RT-qPCR) with TaqMan[®] Assays and the relative expression (Fold Change, FC) was quantified using a pool of cDNA of normal pituitary glands as calibrator and *TBP*, *PGK1* and *MRPL19* as reference genes. This molecular study found a dominant expression of PRL (FC of PRL: 9.122) compared to the rest of anterior pituitary hormone genes (FC of *GH1*: 0.149; *FSHβ*: 0.231; *LHβ*: 0.092; *TSHβ*: 0.018; *POMC*: 1.001; *AVPR1B*: 0.239, and *CRHR1*: 1.087). According to the median and 25th and 75th percentiles of