

Case Report

Thyroxine replacement by colonic route and absorption kinetics: case report

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ABSTRACT

In the literature there are only 2 reports of replacement of thyroid hormones by colonic route. The objective of this study is to present a clinical case where thyroid hormone replacement was performed through the application of enemas with levothyroxine. 78-year-old patient with hypothyroidism is presented who attended to the emergency room with intestinal occlusion, which presented refractory hypothyroidism secondary to intestinal occlusion and she underwent hormone replacement with enemas with levothyroxine. The kinetics of colonic absorption of thyroid hormones takes twice as long to reach the plateau of serum levels with respect to absorption in jejunum and ileum.

Keywords: Enema, Hypothyroidism, Thyroxine

INTRODUCTION

Thyroid hormone replacement with enemas containing levothyroxine is a valid therapeutic measure in patients with hypothyroidism secondary to high intestinal obstruction. Here, we present the case of a patient with refractory hypothyroidism who underwent thyroid hormone replacement through enemas with levothyroxine. The primary absorption site for levothyroxine is the jejunum and ileum (53%).¹⁻³ Certain conditions can disrupt the absorption of free T4 (FT4), preventing the normalization of TSH levels.⁴ High intestinal obstruction impedes drug absorption despite proper administration. The colonic route of administration plays a significant role in drugs designed for local action in conditions such as inflammatory bowel disease.⁵ Despite factors that may hinder proper colonic drug absorption, such as tight cell junctions or reduced surface area, there are two case reports describe the therapeutic use of levothyroxine enemas in refractory

hypothyroidism patients with contraindications for oral administration.⁶⁻⁸

CASE REPORT

A 78-year-old female patient presented with hypothyroidism secondary to iodine radioablation for unspecified goiter diagnosed and treated in 1986. Since then, she had been managed with 150 mcg of levothyroxine every 24 hours with poor administration technique. The patient had a history of inguinal hernia repair (1970), two cesarean (1972, 1977), a hysterectomy (1996), and a low anterior resection with colo-anal anastomosis secondary to rectal tumor (2018). She came to the emergency department in November 2022 due to high intestinal obstruction secondary to gastric volvulus diagnosed by tomography and confirmed by upper esophagogastric series (Figure 1).



Figure 1: Esophagogastric series demonstrating gastric volvulus as the cause of high obstruction preventing the absorption of levothyroxine in the jejunum and ileum.

The proposed management for gastric volvulus was to consider placing a percutaneous gastrostomy tube endoscopically. However, thyroid function tests reported the following levels: TSH 36.48 mIU/ml, T4T 2.96 ug/dl, FT4 0.34 ng/dl, T3T 0.0 ng/ml, FT3 1.95 pg/ml (Reference: TSH: 0.38-5.33 mIU/ml, T4T: 6.09-12.23 ng/ml, FT4: 0.58-1.64 ng/dl, T3T: 0.87-1.78 pg/ml, FT3: 2.39-6.79 pg/ml). Due to these abnormal thyroid function levels, any invasive procedure was postponed by the

anesthesiology team. Thyroid hormone replacement was initiated with a loading dose of 300 mcg of levothyroxine orally and 100 mg of hydrocortisone every 8 hours with a clamped nasogastric tube 1 hour after ingestion for 3 days. Thyroid hormone levels did not show significant elevation in control labs at 24 and 48 hours. Liothyronine 10 mcg orally was added, and the levothyroxine dose was increased to 500 mcg with strict clamping of the nasogastric tube, but there was no favorable response in thyroid function tests. Due to the unavailability of intravenous levothyroxine in the country, an enema with 1000 mcg of levothyroxine in 300 ml of 0.9% saline solution was administered, and serum levels of thyroid hormones were monitored throughout the day (Table 1).

Table 1: Absorption kinetics of enema with 1000 mcg of levothyroxine (ng/dl).

Sample time (hours)	T4L (ng/dl)
11.52	0.37
13.33	0.54
14.30	0.69
15.30	0.71
17.43	0.72

T4L: 0.36 ng/dl (basal level). Laboratory reference values at the General Hospital of Mexico: T4L: 0.58-1.64 ng/dl.

With an adequate response, an enema was indicated every 24 hours with good tolerance. Colonic hormone replacement was achieved by colonic absorption after 3 weeks (Figure 2).

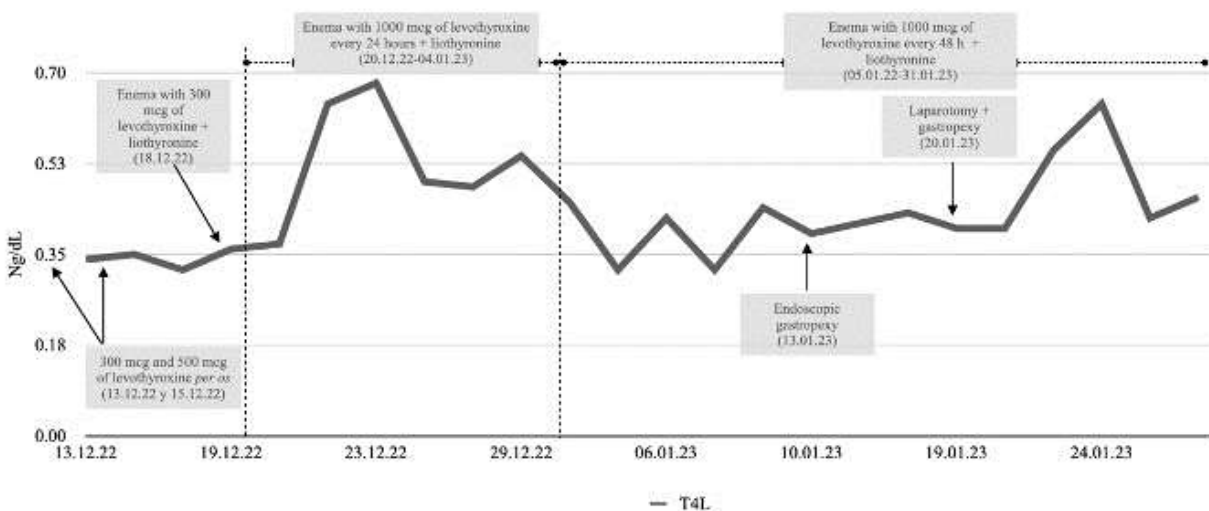


Figure 2: Curve of free T4 levels in relation to thyroid hormone replacement via oral and with the administration of enemas with levothyroxine.

Clinically, the patient showed improved alertness, well-hydrated mucous membranes and skin, with no hemodynamic or ventilatory compromise. The patient underwent endoscopy for gastropexy as a management for gastric volvulus without success. Subsequently, laparotomy was performed for gastropexy with a torpid evolution. Postoperatively, the patient had partial oral

tolerance due to abdominal distension, possibly secondary to postoperative ileus. The patient experienced respiratory difficulty, leading to admission to the Intensive Care Unit with poor ventilatory progression. Due to acute respiratory distress, the patient suffered a cardiopulmonary arrest on January 31, 2023, without return of spontaneous circulation.

DISCUSSION

The prevalence of hypothyroidism in the general population is 5%. FT4 replacement is recommended as the sole treatment.¹ Primary refractory hypothyroidism refers to patients who persist with hypothyroidism despite high doses of levothyroxine, meaning elevated TSH levels despite a levothyroxine dose >1.9 mcg/kg.⁹ Conditions that alter levothyroxine absorption can prevent the normalization of TSH levels.¹ This work presents a patient with subacute gastric volvulus, an unusual cause of malabsorption, coupled with the patient's poor technique in taking sodium levothyroxine, these factors could have contributed to refractory hypothyroidism before her hospitalization. Other organic causes leading to persistent hypothyroidism despite adequate medication include concurrent medications (such as ferrous sulfate, calcium carbonate, antacids), functional gastrointestinal disorders (celiac disease, atrophic gastritis, tropical sprue, intestinal resection, diarrhea), and drug-modified pharmacokinetics or pharmacodynamics (rifampicin, carbamazepine, phenytoin, amiodarone), as well as anti-T4 antibodies.¹⁰

First-line treatment for refractory hypothyroidism

Levothyroxine is the first-choice drug for managing deficiencies in thyroid hormones.¹¹ It is the levorotatory isomer of thyroxine (T4), an amino acid-derived compound containing iodine embedded in a glycoprotein called thyroglobulin. This synthetic derivative is identical to the natural hormone and is indistinguishable in biochemical and physiological terms from the natural form.^{2,10} Gastric volvulus results in the inability of levothyroxine sodium to reach the site in the gastrointestinal tract where it is normally absorbed. Initially, hormone replacement was attempted orally; however, due to the obstructive condition, serum levels of free thyroxine (FT4) and thyroid-stimulating hormone (TSH) did not improve.

The primary absorption site for levothyroxine is the small intestine, specifically the duodenum (15%), jejunum, and ileum (53%), with minimal absorption in the stomach.¹⁻³ On average, 70% of levothyroxine is absorbed, requiring an acidic pH for optimal dissolution.¹ As part of the patient's management, liothyronine (FT3) was prescribed as an adjuvant method, resulting in partial improvement in serum levels. Approximately 79-90 mcg of T4 and 15-30 mcg of T3 are produced daily, but T3 production is insufficient to meet the body's requirements. Therefore, 80% of the body relies on the peripheral conversion of T4 to T3. Both T4 and T3 are active, but T3 is more active as nuclear receptors have 10 times greater affinity for T3.²

Colon administration of thyroid hormones

Due to the patient's age group, it is reported that in geriatric patients, the intestinal absorption of T4 is slightly reduced, and its catabolism to triiodothyronine is

decreased.¹¹ However, due to the gastric volvulus that conditions refractory hypothyroidism, an evaluation by the Thyroid Clinic was requested, who indicated loading doses without response. Subsequently, due to the absence of intravenous levothyroxine in the country, the colonic route was chosen. The colon is a storage organ whose goal is to absorb water and electrolytes. Colonic transit represents 90% of all intestinal transit but is extremely variable and characterized by segmental movements.¹²

The distribution of the drug varies depending on the transrectal dose applied and depends on capacity and retention time.⁵ Solubility and dose are important factors for colonic bioavailability.⁵ Colonic absorption is not selective for ions; it is paracellular, and liquid absorption follows the osmotic gradient generated by sodium transcellular absorption.¹² Rectal administration of medications can be with suppositories or enemas, although it is not always effective due to the high variability of drug distribution by this route.⁶ At the colonic level, drug absorption is passive via a paracellular route. Factors favoring colonic drug absorption include slow transit, which allows the drug to be in contact with the mucosa for a longer period than in the small intestine. Factors hindering adequate colonic drug absorption are tight cell junctions, small surface area, wide diameter, high viscosity of content delaying absorption.⁶ Factors modifying the pharmacokinetics and pharmacodynamics of a drug include pH, which in the colon is determined by carbohydrate fermentation. More fermentation leads to lower pH and vice versa.^{5,6,13}

Kinetics of levothyroxine absorption was performed on the day of 1000 mcg levothyroxine enema administration, where after 4 hours of enema administration, FT4 levels reached a plateau. The time to peak concentration in more than 70% is at 2 hours in euthyroid individuals and 3 hours in hypothyroid individuals, and food delays the time to peak concentration. The bioavailability of levothyroxine is 60-80% in euthyroid individuals.^{2,9-11} It is noteworthy that the intestinal absorption of levothyroxine increases linearly in the first 60-90% before reaching a plateau.¹⁰ The ionization state of sodium levothyroxine and the dissolution properties of pharmaceutical preparations are influenced by variations in intraluminal pH.¹¹

In the colon, pH depends on carbohydrate fermentation carried out by normal microbiota, mainly in the proximal colon. Thus, in the ascending colon, the pH tends to be lower than in the descending colon.⁶ The absorption capacity of levothyroxine decreases with increasing pH.¹¹ Therefore, colonic absorption is expected to be slower and less effective, requiring a higher drug dose compared to oral administration. There are physiological factors that make the colonic route of drug administration less than ideal. However, adequate absorption of levothyroxine was achieved as reported in control follow-up tests. In the literature, there are two case reports where enemas with levothyroxine are used as a method of

thyroid hormone replacement in patients for whom oral administration is not feasible.

CONCLUSION

Replacement of thyroid hormones with enemas containing levothyroxine is a valid and safe therapeutic measure in patients with hypothyroidism secondary to high intestinal obstruction. The absorption kinetics of solid levothyroxine administered via the colonic route is initially linear until reaching a plateau, very similar to the absorption kinetics in the small intestine but differing in that the time to reach the plateau is doubled (2 vs. 4 hours, respectively), possibly related to physiological factors such as a smaller absorption surface, tight cell junctions, or non-selective ionic transport. High intestinal obstruction is a cause of refractory hypothyroidism because it prevents the absorption of levothyroxine in the jejunum and ileum, where more than 70% of the drug is absorbed.

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REFERENCES

1. Benvenga S, Di Bari F. Intestinal absorption and buccal absorption of liquid levothyroxine. *Endocrine*. 2017;58(3):591-4.
2. Colucci P. Review of the pharmacokinetics of levothyroxine for the treatment of hypothyroidism. *Eur Endocrinol*. 2013;9(1):40-7.
3. Gadiraju S, Lee CJ, Cooper DS. Levothyroxine dosing following bariatric surgery. *Obes Surg*. 2016;26(10):2538-42.
4. Catalina PF, Carpio D. 2015. Levothyroxine malabsorption. *Med Clin*. 2015;145(1):46.
5. Amidon S, Brown JE, Dave VS. Colon-targeted oral drug delivery systems design trends and approaches. *AAPS Pharm Sci Tech*. 2015;16(4):731-41.
6. Patel M, Shah T, Amin A. Therapeutic opportunities in colon-specific drug-delivery systems. *Crit Rev Ther Drug Carrier Syst*. 2007;24(2):147-202.
7. Obeidat KA, Saadeh NA, As'ad A, Bakkar S. Successful Management of Hypothyroidism in Gastric Outlet Obstruction Using Levothyroxine Rectal Enemas. *Am J Case Rep*. 2018;19:903-5.
8. Ybarra M, Dos Santos TJ, Cabido CT, Dichtchekenian V, Damiani D. rectal levothyroxine for the treatment of hypothyroidism a case study. *Pediatrics*. 2018;142(2):e20173317.
9. Gonzales KM, Stan MN, Morris JC, Bernet V, Castro MR. The levothyroxine absorption test. *Thyroid*. 2019;29(12):1734-42.
10. Ghosh S, Pramanik S, Biswas K, Bhattacharjee K, Sarkar R, Chowdhury S, et al. Levothyroxine absorption test to differentiate pseudomalabsorption from true malabsorption. *Eur Thyroid J*. 2020;9(1):19-24.
11. Ianiro G, Mangiola F, Di Rienzo TA, Bibbò S, Franceschi F, Greco AV, Gasbarrini A. Levothyroxine absorption in health and disease, and new therapeutic perspectives. *Eur Rev Med Pharmacol Sci*. 2014;18(4):451-6.
12. Milla PJ. Advances in understanding colonic function. *J Pediatr Gastroenterol Nutr*. 2009;48(2):S43-5.
13. Geibel JP. Secretion and absorption by colonic crypts. *Annu Rev Physiol*. 2005;67:471-90.

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