Factors Affecting Gastrointestinal Absorption of Levothyroxine: A Review

Marko Skelin, M.Pharm[1]; Tomo Lucijanić, MD[2]; Daniela Amidžić Klarić, M.Pharm, PhD[3]; Arnes Rešić, MD[4]; Miro Bakula, MD, PhD[5]; Ana-Marija Liberati-Čizmek, MD[5]; Hossein Gharib, MD, PhD[6]; and Dario Rahelić, MD, PhD[2]

[1]Pharmacy Department, General Hospital Šibenik, Šibenik, Croatia; [2]Department of Endocrinology, Diabetes and Metabolic Disorders, Clinical Hospital Dubrava, Zagreb, Croatia; [3]Department of Health Ecology, Public Health Brčko DC, Brčko DC, Bosnia and Herzegovina; [4]Department of Paediatrics, Children's Hospital Zagreb, Zagreb, Croatia; [5]Department of Endocrinology, Diabetes and Metabolic Disorders, General Hospital "Sv. Duh," Zagreb, Croatia; and [6]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic College of Medicine, Rochester, Minnesota

ABSTRACT

Purpose: Levothyroxine (LT4) is a drug with a narrow therapeutic index, applied in small amounts (micrograms), which makes interactions in the absorption phase clinically significant. The main aim of this article was to review and present the latest information on factors that affect the gastrointestinal absorption of this drug.

Methods: Relevant data were collected by using the MEDLINE, PubMed, EMBASE, Web of Science, Science Direct, and Scopus databases with the key words *levothyroxine* and *absorption*. Searches were not limited to specific publication types, study designs, dates, or languages. The reports were highly variable in the amount of information provided regarding study design and methods. Because of the heterogeneity of studies, no statistical analysis was performed.

Findings: Many gastrointestinal disorders, such as celiac disease, atrophic gastritis, lactose intolerance, and *Helicobacter pylori* infection, may impede the absorption of levothyroxine. During treatment of these disorders, it is necessary to monitor serum thyroid-stimulating hormone and free T4 values to reduce the risk of developing iatrogenic hyperthyroidism. Soybeans and coffee have the greatest impact on the reduction of absorption, whereas vitamin C has the ability to increase it. Conversely, the effect of dietary fiber on the absorption of LT4 is not yet fully understood; further research is needed on this topic. A decrease in the absorption of LT4 is established and clinically significant when administered concomitantly with cholestyramine, colesevelam, lanthanum, calcium carbonate, calcium citrate, calcium acetate, iron sulfate, ciprofloxacin, aluminum hydroxide, sevelamer, or proton pump inhibitors. This effect should be taken into consideration when prescribing these drugs concomitantly with LT4. The effects of *Giardia lamblia* infection and the influence of orlistat, polystyrene sulfonate, raloxifene, and simethicone on absorption of LT4 have been poorly documented. For bariatric surgery, sucralfate and H_2-antagonist interactions are not well founded or contradictory evidence is available regarding their existence; additional research should be conducted.

Implications: The majority of the interactions are clinically significant. They are based on the LT4 adsorption on interfering substances in the digestive tract, as well as a consequently reduced amount of the drug available for absorption. These interactions can be avoided by separating the administration of LT4 and the interfering substance. (*Clin Ther.* 2017;39:378–403) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: absorption, GI diseases, interactions, levothyroxine.

Accepted for publication January 3, 2017.
http://dx.doi.org/10.1016/j.clinthera.2017.01.005
0149-2918/$ - see front matter

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INTRODUCTION

Since the 1960s, levothyroxine, a synthetic L-isomer of thyroxine (LT4), has become the gold standard in the treatment of hypothyroidism. This narrow therapeutic index drug is most often orally administered as a tablet in low doses (micrograms). The absorption of levothyroxine from the gastrointestinal (GI) tract is one of the critical steps leading up to its pharmacologic effect. Orally ingested LT4 is absorbed through the intestinal mucosa, especially in the jejunum and ileum. Approximately 60% to 82% of the administered dose is mostly absorbed during the 3 hours after administration of the drug.[1–7] The numerous factors that alter the rate and extent of oral drug absorption can be divided into 3 main categories: physiologic, physicochemical, and biopharmaceutical. Physiologic factors that significantly affect oral LT4 absorption are GI anatomy and physiology, GI transit time, the GI pH, and influence of intestinal drug transporters.[8] Because the stomach is the primary site of tablet disintegration and dissolution of drugs from the oral formulation, while the small intestine is the major site of levothyroxine absorption, diseases of those parts of the GI tract can affect the pharmacokinetic profile of the drug, and consequently, the treatment outcome.[8,9]

Concomitant orally administered drugs and food intake can significantly affect the bioavailability of LT4, including the beginning, rate, and extent of absorption. The influence of food on its oral drug bioavailability depends on the physical–chemical properties of drug molecules, the oral dosage form, the amount and composition of meals, the order and time interval between the food and drug administration, and the condition of the digestive system.[8,9]

In recent years, the Biopharmaceutical Drug Disposition Classification System has been used for the prediction of complex food effects on the oral bioavailability of drugs. According to this classification, drugs are characterized into 4 classes on the basis of their solubility, permeability, and metabolism; levothyroxine is categorized as class III.[9] The drugs of this class have a high solubility but a low permeability, and their uptake often includes influx as well as efflux transporters. According to the available literature, the active transport of thyroxine into cells has been recognized, and in vivo studies have shown that the organic anion transporting polypeptide transporter is involved at different levels on the LT4 absorption.[10,11]

Furthermore, it is important to point out that drug–drug interactions are one of the most common causes of medication errors in developed countries, particularly in elderly patients due to polytherapy. Medication errors are an important problem of the health system and have a large impact on the effectiveness and costs of treatment.[12] A literature survey revealed numerous examples of the impact of drugs on the oral bioavailability of levothyroxine, which is especially important due to its narrow therapeutic index. It can consequently have an impact on the effectiveness of the treatment.

Because the oral drug bioavailability is one of the major causes of LT4 therapeutic variability, the main aim of the present review was to systematically demonstrate the occurrences and mechanisms of the influence of food, drugs, and certain GI disorders on the absorption of levothyroxine and, consequently, treatment outcomes. It should be noted that in the last few years, the attention of scientists has been mainly focused on new oral dosage forms of levothyroxine. Also, this study discusses the impact of other factors, such as formulation and time of administration, on the pharmacokinetic profile of levothyroxine. In the available literature, some investigators[1,3–5] described multiple conditions and medications that affect the absorption of LT4. Conversely, hypothyroidism, a common chronic disorder, is managed by many specialists, including endocrinologists, internists, primary care physicians, surgeons, and pediatricians, who would likely be interested in an update on thyroxine therapy. For all of these reasons, the purpose of the present review was to provide an update on thyroxine therapy, with an emphasis on the new pharmaceutical formulations, as well as recent information on the types and mechanisms of interference of LT4 GI absorption by commonly used drugs.

MATERIALS AND METHODS

All relevant scientific literature was used for preparing this review, and the primary end point was the factors affecting the GI absorption of levothyroxine. To our study goal, relevant data were collected by using the MEDLINE, PubMed, EMBASE, Web of Science, ScienceDirect, and Scopus databases. The literature search process was conducted by using the key words *levothyroxine* and *absorption*. The literature was

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