

Hypothyroidism Resulting From Generic Levothyroxine Failure

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Abstract: In today's cost-conscious health care system, generic preparations should be prescribed whenever possible provided that safety and efficacy are not compromised. Several reports, however, suggest that generic levothyroxine may not always be interchangeable with the proprietary preparations. Such interchangeability is critical because patients are likely to receive different brands of levothyroxine during the life of their treatment. We report a case of severe hypothyroidism that developed in a patient who had been well controlled before receiving a generic levothyroxine preparation. Analysis of the patient's tablet by high-pressure liquid chromatography showed that the levothyroxine content was approximately 30 percent less than its labeled content and outside current Food and Drug Administration (FDA) requirements. It is likely that poor tablet bioavailability was a contributory factor. Euthyroidism was achieved with the same dose of a more potent and possibly more bioavailable brand-name product. Until levothyroxine products become more uniform and the FDA confers therapeutic equivalence, product substitution with expense as the principal consideration should be avoided. (J Am Board Fam Pract 1991; 4:167-70.)

Synthetic levothyroxine sodium is widely accepted as the preparation of choice for the management of hypothyroidism, as well as for suppression of the thyroid-pituitary axis. Levothyroxine sodium is believed to be a more reliable and consistent product than the less expensive desiccated thyroid extract, which may contain too much or too little active hormone.¹ Levothyroxine is also preferred over triiodothyronine (T₃) for several reasons. T₃ is more expensive, requires multiple daily dosing because of its short half-life to insure a uniform response, and is associated with supraphysiologic elevations in plasma T₃ levels, which can produce thyrotoxic symptoms in predisposed patients. Brand-name levothyroxine preparations are deemed therapeutically similar but not bioequivalent.^{2,3} Several reports, however, suggest that generic levothyroxine, like generic digoxin, sustained-release theophylline, phenytoin, and thioridazine, are not always interchangeable with brand-name preparations.⁴⁻⁷ Such interchangeability is critical because patients are likely to receive different brands over the life of their treatment.

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Case Report

A 34-year-old white woman was referred to our thyroid clinic in 1985 for further evaluation of her medullary thyroid carcinoma. In early 1984, she noticed a lump in her throat. She had no symptoms of hyperthyroidism or hypothyroidism and denied any family history of thyroid disease or history of childhood thyroid irradiation. Her thyroid function tests were normal, and there was no other significant medical history. In June 1984, a fine-needle biopsy of the firm 1-cm movable midline nodule showed medullary carcinoma. Soon after the biopsy, dissection of the left side of the neck and a left hemithyroidectomy confirmed the diagnosis of medullary carcinoma. Multiple nodes were positive. Calcitonin levels remained persistently elevated postoperatively, indicating residual medullary carcinoma, and further surgery was scheduled. In November 1984, a right hemithyroidectomy and dissection of the neck and mediastinum were done uneventfully, again with the finding of medullary carcinoma with metastasis to multiple nodes. No residual thyroid or adenopathy was palpable on physical examination. Postoperatively, the patient received levothyroxine therapy, 0.1 mg daily, to maintain a euthyroid state and to suppress any remaining residual thyroid tissue. Her physical examination and thyroid function tests remained normal. Serum calcitonin levels, however, remained per-

sistently elevated to more than 3000 ng/L (3000 pg/mL). There was no evidence of functioning thyroid tissue on imaging with iodine (I^{123}) and dimethylsuccinate. Magnetic resonance imaging (MRI) in March 1985 showed abnormal tissue in the right side of the neck, but needle biopsies of this area on two separate occasions showed only scar tissue. A follow-up MRI in 1986 and in 1988 also showed no additional changes. Further surgical exploration was not performed. The patient was then referred back to her endocrinologist for management in her own community.

The patient remained well and euthyroid while receiving 0.1 mg levothyroxine daily until August 1988, when mild hypothyroid symptoms of fatigue and cold intolerance were noted on a routine clinic visit. Laboratory findings confirmed the presence of hypothyroidism, although she indicated strict compliance with her daily dose of 0.1 mg levothyroxine. She used no other medication except levothyroxine; however, her last prescription for levothyroxine was filled in July 1988 with a generic levothyroxine preparation at a pharmacy closer to her home. One month later, the thyroxine (T_4) level dropped from a normal average of 130 nmol/L (10.1 μ g/dL) to 38.6 nmol/L (3.0 μ g/dL), the free thyroxine index decreased from 3.0 when normal was 1.3 to 4.2 to 3.2 when normal was 6.5 to 12.5, and thyroid-stimulating hormone (TSH) levels rose from an average of 1 mU/L (1 μ U/mL) to 94 mU/L (94 μ U/mL) (Figure 1). Complete resolution of hypothyroid symptoms occurred after the patient received 0.1 mg daily of a brand-name levothyroxine preparation (SynthroidTM) at the end of August. Thyroid function tests obtained by her private physician and later by us in early January 1989 showed a normal T_4 level of 113 nmol/L (8.8 μ g/dL), a free thyroxine index of 10.1, and suppression of the TSH level to 0.17 mU/L (0.17 μ U/mL). The patient remained clinically and chemically euthyroid on further visits.

The patient's prescription vial, dated 5 July 1988 contained generic levothyroxine, manufactured by Pharmaceutical Basics and distributed by United Research Laboratories, with an expiration date of January 1990. In September 1988, two sets of 20 tablets taken from the patient's prescription vial were crushed, sonicated, and analyzed by high-pressure liquid chromatography (HPLC).

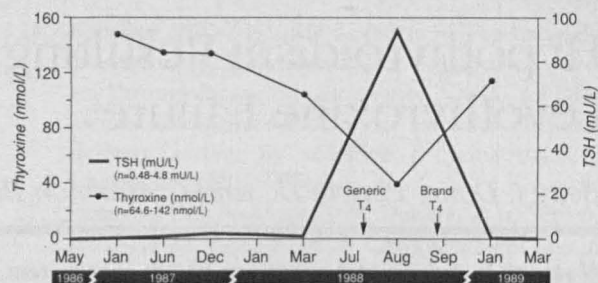


Figure 1. Hypothyroidism resulting from generic levothyroxine failure.

The analysis of the two tablet batches showed a levothyroxine tablet content of 71.4 and 69.7 μ g, respectively. The analysis was carried out by the Clinical Research Unit of the Division of Clinical Pharmacy.

Discussion

We report this case to heighten awareness of continuing potency and bioavailability problems with generic levothyroxine preparations. Our patient developed severe hypothyroidism following replacement with a subpotent generic levothyroxine product. She had been well controlled for more than 2 years with 0.1 mg levothyroxine daily until she was changed to a generic preparation. She indicated strict compliance in taking her levothyroxine, had not received any other medications, and had no medical conditions that could have affected the absorption or metabolism of levothyroxine.

Several factors could have contributed to the failure of this generic levothyroxine product. The most critical factor for our patient was tablet potency. Tablet analysis by HPLC assay showed that the levothyroxine content was approximately 30 percent less than its labeled content and outside the U.S. Pharmacopeia (USP) requirements that the tablet contain 90 to 110 percent of its stated content. The tablet content of the brand-name product given our patient was not analyzed because several prior analyses have shown that since its reformulation in 1982, it contains almost 100 percent of its labeled claim.^{2,3,6,8} In addition, limited bioavailability of the generic preparation caused by poor or reduced absorption of thyroxine from the gut could have been a contributory factor. Levothyroxine absorption can vary from person to person, but it also depends on how readily thyroxine is released from each manufacturer's tablet formulation. Unfortunately,

the bioavailability of generic levothyroxine preparations has not been well studied because in vivo bioavailability studies are not required for marketing. Our patient was changed to a proprietary levothyroxine product with a known bioavailability of 81 percent after its reformulation in 1982.⁶ Finally, a possible cause is the shelf life of the tablet. Levothyroxine tablets have been reported to lose thyroxine at a rate of 5 percent per year.⁹ Our patient's tablets were not outdated (January 1990 expiration date), so this explanation is unlikely unless there was an increase in the rate of loss. In our patient, euthyroidism was achieved with the same dose of a more potent and perhaps a more bioavailable product.

Generic preparations have been reported to contain less levothyroxine than stated on the label.^{4,7} In 1980, Stoffer and Szpunar⁴ noted that generic levothyroxine sodium tablets are not always equal in potency to the brand-name products. Similar findings of deficient and excessive levothyroxine tablet contents, varying from 34 to 126 percent of the label claim, also have been reported.⁵⁻⁷ Conversely, brand-name products now contain close to 100 percent of their labeled claim.^{2,3,6,8} To ensure levothyroxine product uniformity, the USP in 1986 required manufacturers to use high-performance liquid chromatography to monitor the tablet levothyroxine content.⁹ Nevertheless, regardless of these new USP modifications, recent reports indicate that tablet potency can be an ongoing and unresolved problem. One generic product had 34 percent⁶ and another tablet had 47 percent⁷ of expected tablet content. Most brand-name manufacturers have adopted these USP recommendations to produce more consistent and potent products. When using more reliable preparations, it appears justified to start with lower thyroxine replacement doses (1.6 to 1.7 $\mu\text{g/kg}$) than previously recommended.⁶ In any case, routine monitoring of patients on any brand of levothyroxine therapy is essential.

Currently, generic levothyroxine is produced by only one manufacturer, Pharmaceutical Basics (PBI), although it is distributed under a wide variety of labels. PBI manufactured the tablet given our patient. In January 1988, another manufacturer, Chelsea Laboratories, which formerly produced levothyroxine under the Rugby

label, ceased production. Rugby Laboratories continues to distribute levothyroxine, but it is now under the PBI label. Two brand-name levothyroxine preparations, manufactured by Boots-Flint (Synthroid[™]) and Rorer Pharmaceuticals (Levothroid[™]), are deemed therapeutically similar but not bioequivalent.^{2,3} A relative newcomer to the brand-name market is Daniels Pharmaceuticals (Levoxine[™]). A double-blind, randomized study comparing two brand-name products (Levoxine[™] and Synthroid[™]) concluded that the two were bioequivalent¹⁰; however, this study suffers from serious methodological and statistical errors and should not be used to substantiate their bioequivalence.¹¹

These difficulties surround sodium levothyroxine products because thyroid preparations existed before 1938, when the Food and Drug Administration (FDA) requirements for preapproval were first enacted and, therefore, enjoy "grandfather" status. The FDA does not recognize levothyroxine products as bioequivalent and interchangeable and, therefore, does not list them in their *Approved Drug Products with Therapeutic Equivalence Evaluation Book* ("Orange Book"). Thus, physicians and pharmacists are required to exercise their professional judgment to select a high-quality product for their patients. Unfortunately, this information is poorly documented and rarely accessible to either the practicing physician or pharmacist. Nevertheless, third-party payments, diagnosis-related groups (DRGs), capitation of reimbursement, and restrictive formularies all insure the healthy existence and continued growth of generic preparations in today's cost-conscious health care system. The cost savings between a generic and brand-name preparation can be substantial. For example, the cost to the pharmacy for 100 tablets of levothyroxine (0.1 mg) from a brand-name manufacturer is approximately \$14.50, while the acquisition costs for the same generic product is only \$5. We do support prescribing the least costly medication if safety and efficacy are not compromised. It is, therefore, essential that generic and brand-name products be interchangeable to prevent loss of clinical efficacy or production of clinical toxicity when patients are unknowingly switched from brand-name to generic products or vice versa. Ideally, patients should be managed with the same brand-name or generic preparation

that has consistently produced a therapeutic success.

Conclusion

Brand-name and generic levothyroxine tablets are not bioequivalent and interchangeable. This case illustrates that serious clinical problems can result from significant differences between the generic and brand-name preparations. Until levothyroxine products become uniform and the FDA confers therapeutic equivalence, product substitution in which expense is the only consideration should be avoided.

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