International Journal of Basic & Clinical Pharmacology
Biswas SA et al. Int J Basic Clin Pharmacol. 2022 Sep;11(5):373-377
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20221817

Original Research Article

Assessment of the pharmacokinetics, safety, and tolerability of levothyroxine sodium in healthy Indian volunteers

Swati A. Biswas[1]*, Anadya Prakash Tripathi[1], Dyotona Sen-Roy[2]

[1]Abbott Healthcare Private Limited, Mumbai, Maharashtra, India
[2]Abbott India Limited, Mumbai, Maharashtra, India

Received: 18 April 2022
Revised: 01 July 2022
Accepted: 06 July 2022

***Correspondence:**
Dr. Swati A. Biswas,
Email: swati.biswas@abbott.com

ABSTRACT

Background: Few studies have assessed the pharmacokinetics of various marketed formulations of levothyroxine available in the Indian market. Here, we assessed the pharmacokinetics and safety of Thyronorm® 100 in healthy Indian volunteers.
Methods: The primary and secondary objectives were to determine the pharmacokinetic profile and to monitor safety and tolerability of 600 µg of levothyroxine, respectively. Eligible subjects received a single oral dose of 6×100 µg of levothyroxine, and pharmacokinetic profiles were monitored up to 432 hours post-dose. Safety assessments included exposure of study drug and incidence of adverse events (AEs) and serious AEs. The mean plasma concentration of LT4 versus time profile was presented on both untransformed and log-transformed scales.
Results: Of 20 enrolled subjects, 1 was discontinued due to an AE of pain, unrelated to study drug. The mean [standard deviation (SD)] age and body mass index of subjects were 35.7 (6.33) years and 25.0 (3.0) kg/m^2, respectively. Following baseline correction, the mean maximum observed drug concentration (C_{max}) and area under the plasma concentration-time curve measured to the last quantifiable concentration (AUC_{0-t}) of free thyroxine were found to be 68.4 (12.09) ng/ml and 6760.0 (2065.05) ng×hr/ml, respectively, with an elimination half-life ($t_{1/2}$) of 205.6 (180.26) hrs and a residual area of 24.6%. The median time to first observed maximum drug concentration (T_{max}) was 2.5 (1.5-2.5) hrs.
Conclusions: These parameters were in accordance with those of other marketed formulations and confirmed the pharmacokinetics and safety of Thyronorm® 100 in healthy volunteers from India.

Keywords: Levothyroxine, Intra-subject variability, Therapeutic index

INTRODUCTION

Primary hypothyroidism is a common endocrine disease with a global prevalence ranging from 0.3% to 5.8%.[1] A nationwide epidemiological study found its prevalence in the Indian population to be substantially higher at 10.95%.[2] Levothyroxine sodium (LT4) is the treatment of choice for hypothyroidism, but efficacy of different marketed formulations is known to vary because of the narrow therapeutic index (NTI) of LT4. At doses only 25% greater or less than optimal, patients may be at risk for iatrogenic hyperthyroidism or hypothyroidism depending on their endogenous thyroid stimulating hormone (TSH) levels.[3]

Moreover, LT4 is physiologically and biochemically indistinguishable from endogenous thyroxine, which may interfere with dose titration needed to achieve the desired therapeutic effect.[3] Therefore, significant proportion of patients have been found to receive inadequate or excessive doses based on having out-of-range endogenous TSH levels. Findings from a cross-sectional, single visit, observational study conducted across 10 cities in India and

involving 1950 adult patients with primary hypothyroidism suggest that as high as 54% of patients had out-of-range serum TSH despite being on LT4 treatment for at least 2 months.[4] Various clinical practice guidelines therefore recommend that patients not change their individual marketed formulations during therapy because switching requires careful recalibration of dose to achieve the necessary therapeutic effect.[5]

Although numerous LT4 formulations have been available in the Indian market for several years, very few studies have been conducted to evaluate the pharmacokinetics and bioequivalence of synthetic levothyroxine in Indian subjects.[6]

Here, we assess the pharmacokinetic and safety of Thyronorm® 100 (LT4 tablets IP 100 µg×6) of Abbott India Limited in healthy, Indian volunteers.

METHODS

Study design

In this open label, single-arm, single-dose, non-comparative, pharmacokinetic study, healthy, adult volunteers were randomized to receive a single oral dose (6×100 µg) of LT4 tablets [Thyronorm® 100 (LT4 100 µg tablets)] with 240 ml of water at ambient temperature under fasting conditions. The study was conducted at Accutest Research Laboratories (I) Private Limited, Ahmedabad, India, from 28 July 2020 to 16 August 2020 in accordance with the ethical principles of the Declaration of Helsinki consistent with International Committee on Harmonization- good clinical practices guidelines and regulatory guidelines of New Drugs and Clinical Trials Rules 2019 G.S.R. 227 (E) and Central Drugs Standard Control Organisation. All volunteers provided written informed consent before being screened.

Eligibility criteria

Adults aged 18-45 years with a body mass index (BMI) of 18.5-30.0 kg/m^2, with normal findings for baseline history, physical examination, and vital signs, clinically acceptable findings for clinical biochemistry, thyroid function tests, urinalysis, lead electrocardiogram and/or chest X-ray, without a significant history of alcoholism or drug abuse, and willing to abstain from xanthine containing food or beverages or grapefruit juice were included in the study. Key exclusion criteria were subjects with a known history of hypersensitivity to LT4 or any of the excipients and/or related drugs, subjects requiring medication having enzyme-modifying activity for any ailment in the 28 days before dosing day, and subjects who had taken prescription medications or any over-the-counter products with known potential to modify the kinetics/dynamics of thyroxine, within 14 days before dosing day, subjects with any medical or surgical conditions, which might have significantly interfered with the functioning of gastrointestinal tract or blood-forming organs. Attempts were made to enroll both male and female subjects. However, only male subjects consented to participation.

Study objectives and assessments

The primary and secondary objectives were to determine the pharmacokinetic profile and to monitor safety and tolerability of 600 µg of LT4, respectively.

Blood samples (5 ml per sample) were drawn at -0.5, -0.25, and 0.0 hours pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, 48.0, 72.0, 144.0, 288.0, and 432.0 hours post-dose. Serum concentrations of thyroxine (T4) were measured by a validated liquid chromatography-mass spectrometry method. The primary pharmacokinetic parameters assessed were maximum observed drug concentration (C_{max}) and area under the plasma concentration-time curve measured to the last quantifiable concentration (AUC_{0-t}). The secondary pharmacokinetic parameters assessed were AUC_{0-inf} ($AUC_{0-t} + Ct/K_{el}$, where C_t is the last measurable drug concentration and K_{el} is the elimination rate constant), T_{max} (time to first observed maximum drug concentration), AUC_{0-t}/AUC_{0-inf}, residual area [(AUC_{0-inf}-AUC_{0-t})/AUC_{0-inf}], K_{el} (apparent first–order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve, using the method of least square regression), and $t_{1/2}$ (terminal half-life as determined by quotient $0.693/K_{el}$).

Safety assessments included exposure of study drug and incidence of adverse events (AEs) and serious AEs.

Statistical analysis

All pharmacokinetic analyses were performed using SAS® version 9.4. Missing sample values of the concentration data were treated as 'missing values' for pharmacokinetic and statistical analyses. The mean plasma concentration of levothyroxine versus time profile was presented on both untransformed and log-transformed scales. This being an exploratory study, formal sample size estimation was not done.

Nevertheless, in line with sample size recommendations for bioequivalence studies, a sample size 20 subjects was considered adequate for this pilot study.[7] Patient demographics and pharmacokinetic parameters were reported as mean [standard deviation (SD)].

RESULTS

Demographics and baseline characteristics

A total of 41 volunteers were screened, out of which 20 who met the eligibility criteria were enrolled, randomized, and received the study drug. One subject was discontinued due to an adverse event of pain over right shoulder. Thus, 19 subjects completed the study.

The mean (SD) age and BMI of the 19 subjects who completed the study were 35.7 (6.33) years and 25.0 (3.0) kg/m^2, respectively.

Pharmacokinetics of levothyroxine

The pharmacokinetics of LT4 as assessed by serum concentrations of thyroxine is shown in Table 1. The mean (SD) baseline uncorrected C_{max} was 140.5 (15.57) ng/ml. The uncorrected exposure was relatively high at 36963.2 (4946.40) ng×hr/ml and 176141.4 (177265.76) ng×hr/ml for AUC_{0-t} and AUC_{0-inf}, respectively, yielding an elimination $t_{1/2}$ of 1290.7 (1562.69) hours, and a residual area of 65.7%. T_{max} was reached at 2.7 (1.11) hrs. Following baseline correction of pharmacokinetic parameters, the mean (SD) C_{max} and AUC_{0-t} of free thyroxine were found to be 68.4 (12.09) ng/ml and 6760.0 (2065.05) ng×hr/ml, respectively, with an elimination $t_{1/2}$ of 205.6 (180.26) hrs and a residual area of 24.6%. The AUC_{0-48} and AUC_{0-72} were 1850.0 (316.46) and 2587.0 (451.9) ng×hr/ml, respectively. The median T_{max} was 2.5 (1.5-2.5) hours. Pharmacokinetic profile of thyroxine following single-dose of LT4 with and without baseline correction is shown in Figure 1.

Safety and tolerability of levothyroxine

LT4 was well tolerated by all subjects. Only one AE was reported over the course of the study. One subject experienced pain over the right shoulder of moderate severity, which was unrelated to study medication and was eventually resolved. No serious AEs were reported.

Table 1: Pharmacokinetics of levothyroxine following single-dose administration in fasted, healthy volunteers.

Mean (SD) N=19	C_{max} (ng/ml)	AUC_{0-t} (ng*hr/ml)	AUC_{0-inf} (ng*hr/ml)	T_{max} (hr)	K_{el} (hr^{-1})	$t_{1/2}$ (hr)	AUC_{0-t}/AUC_{0-inf}	Residual area (%)
Baseline corrected	68.4 (12.09)	6760.0 (2065.05)	10253.6 (5839.41)	2.7 (1.11)	0.005 (0.003)	205.6 (180.26)	75.4 (19.81)	24.6 (19.81)
CV (%)	17.7	30.6		-				
Baseline un-corrected	140.5 (15.57)	36963.2 (4946.40)	176141.4 (177265.76)	2.7 (1.11)	0.001 (0.000)	1290.7 (1562.69)	34.3 (25.23)	65.7 (25.23)
CV (%)	11.1	13.4		-				

Note: AUC_{0-t}, area under the plasma concentration-time curve measured to the last quantifiable concentration; AUC_{0-inf}, AUC_{0-t} + Ct/K_{el}; C_{max}, maximum observed drug concentration; Ct, last measurable drug concentration; CV, coefficient of variation; K_{el}, apparent first-order terminal elimination rate constant (calculated from semi-log plot of the plasma concentration versus time curve using the method of least square regression); residual area, (AUC_{0-inf}-AUC_{0-t})/AUC_{0-inf}; $t_{1/2}$, terminal half-life as determined by quotient 0.693/K_{el}; T_{max}, time to first observed maximum drug concentration.

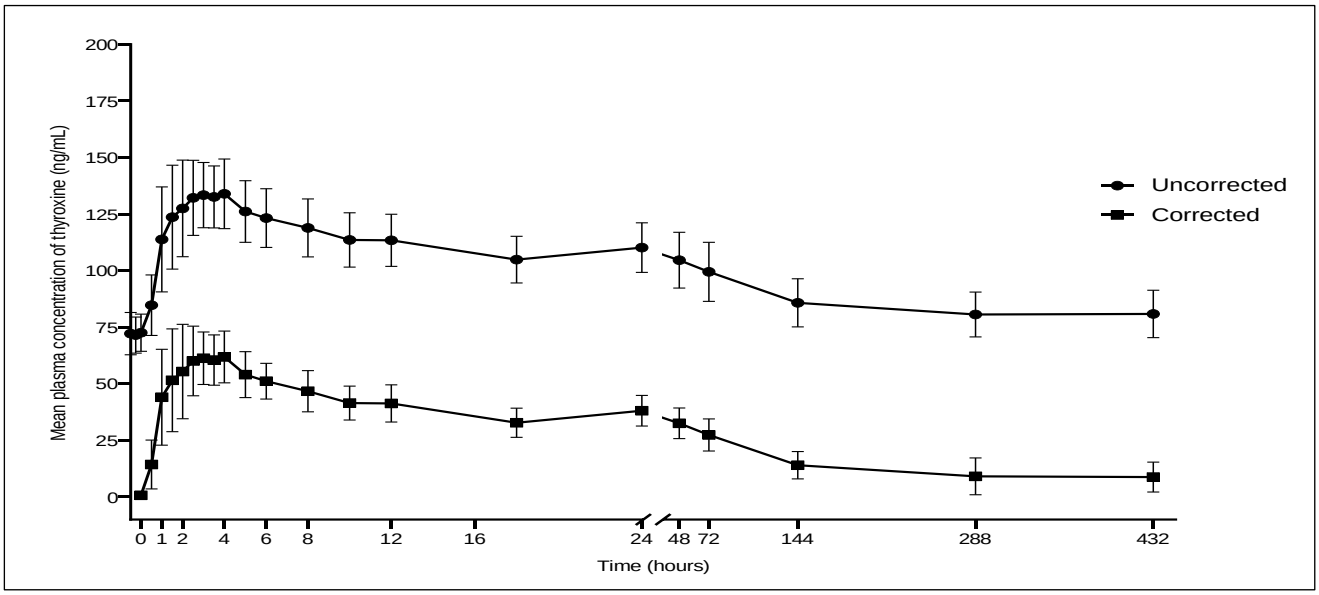

Figure 1: Pharmacokinetic profile of thyroxine following single-dose administration of levothyroxine sodium in fasted healthy volunteers.

Note: Data are represented as baseline-corrected and uncorrected mean (SD) levels of thyroxine from time 0 to 432 hrs following a single oral dose of levothyroxine; SD- standard deviation.

DISCUSSION

In this single-dose, single-arm study, free thyroxine peaked at 2.7 hours and showed a rapid decline in the first 24 hours after which levels stabilized up to 200 hours post-dosing, thereby yielding a prolonged elimination $t_{1/2}$ of 205.6 hrs. The long elimination $t_{1/2}$ and high exposure rates indicate delayed elimination of thyroxine at doses of 600 µg. The substantial differences observed between baseline corrected and uncorrected values of LT4 pharmacokinetic parameters are reflective of normal levels of endogenous thyroxine in the current study population of healthy, euthyroid volunteers. These pharmacokinetic parameters are in accordance with those of other marketed formulations as assessed in various global studies and in one study from India.[6] To date, multiple generic formulations of LT4 have become available and several global studies have compared the pharmacokinetic properties and bioequivalence of these formulations.[3,8,9-13] The purpose of our study was to estimate the pharmacokinetics of a 6×100 µg tables of Thyronorm® as a single-dose of 600 µg in healthy Indian volunteers with a view to establish the relative bioavailability with other formulations and to determine the safety and tolerability of this supratherapeutic dose (600 µg) in healthy volunteers.

Two recent reviews by Concordet et al have highlighted the importance of individual bioequivalence and exposure ratios in determining the suitability of switching between two LT4 formulations.[14,15] The authors based their observations on the findings of an average bioequivalence (ABE) study conducted in France with 204 subjects and a narrow a priori bioequivalence range of 0.90-1.11 to replace an old formulation of Levothyrox® with a new formulation (NF) that only differed in the presence of excipients. Over a year following the launch of the NF, ~1.43% of patients who switched to the NF reported adverse drug reactions. Further analyses revealed that only 23% of analyzed patients were hypothyroid, while 67% had normal TSH status. Retrospective analysis of the previously conducted ABE study further revealed that >50% of patients enrolled were outside the apriori bioequivalence range and that because the NF had an intra-subject variability of 23.7%, more subjects were enrolled to meet the stringent bioequivalence confidence intervals. The coefficient of variation (CV) for Thyronorm® AUC_{0-t} was 30.5% following baseline correction in our study. The US Food and Drug Administration had reported intra-subject variability for LT4 AUC of 9.3% (range, 3.8%-15.5%) from 9 bioequivalence trials.[16] Thus, given the high intra-subject variability observed with various LT4 formulations, and considering that LT4 is an NTI drug, switching formulations may significantly impact safety outcomes.

The limitations of the present study included the single-arm design that prevented true bioequivalence assessment and absence of generalizability to diseased subjects. Nevertheless, prospective studies with crossover design, larger sample sizes, and recruitment of hypothyroid individuals from India will provide further insights into the performance of this formulation.

CONCLUSION

In conclusion, findings from this single-arm, single-dose study suggest that the pharmacokinetic profile of LT4 in the Thyronorm® 100 formulation is consistent with that of other formulations; however, switching of formulations is not recommended given the low NTI and high intra-subject variability of LT4 that may increase the potential for adverse safety outcomes.

ACKNOWLEDGEMENTS

The authors thank Rupanwita Ghosh, Abbott India Limited, for critical review of the manuscript and for medical writing support and editorial assistance.

Funding: The study was funded by Abbott India Limited
Conflict of interest: All authors are employees of Abbott
Ethical approval: The study was conducted in accordance with the ethical principles of the Declaration of Helsinki consistent with International Committee on Harmonization-Good Clinical Practices guidelines and regulatory guidelines of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) and Central Drugs Standard Control Organisation. All volunteers provided written informed consent before being screened

REFERENCES

1. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018;14(5):301-16.
2. Unnikrishnan AG, Kalra S, Sahay RK, Bantwal G, John M, Tewari N. Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. Indian J Endocrinol Metab. 2013;17(4):647-52.
3. Blakesley V, Awni W, Locke C, Ludden T, Granneman GR, Braverman LE. Are bioequivalence studies of levothyroxine sodium formulations in euthyroid volunteers reliable? Thyroid. 2004;14(3):191-200.
4. Mithal A, Dharmalingam M, Tewari N. Are patients with primary hypothyroidism in India receiving appropriate thyroxine replacement? An observational study. Indian J Endocrinol Metab. 2014;18(1):83-8.
5. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid. 2014;24(12):1670-751.
6. Glaxo Smith Kline. Bioequivalence of Two Levothyroxine Tablet Formulations in Healthy Indian Volunteers, 2012. Available at: https://clinicaltrials.gov/ct2/show/record/NCT01536678?view=record. Accessed on 10 April 2022.

7. Bhupathi C, Vajjha VHG. Sample size recommendation for a bioequivalent study. Statistica. 2017;77:65-71.
8. Wuxu Data. Public Assessment Report Decentralised Procedure. Procedure Number: DE/H/5712/001-011/DC Tillomed Laboratories Limited, 2021. Available at: https://file.wuxuwang.com/hma.pdf. Accessed on 10 April 2022.
9. Government of UK. Public Assessment Report Levothyroxine 12.5 microgram Tablets, Levothyroxine 25 microgram Tablets and Levothyroxine 75 microgram Tablets. UK License number: PL 00289/1971-73). TEVA UK Ltd, 2022. Available at: https://www.gov.uk/guidance/find-product-information-about-medicines. Accessed on 10 April 2022.
10. Colucci P, Yue CS, Ducharme M, Benvenga S. A Review of the Pharmacokinetics of Levothyroxine for the Treatment of Hypothyroidism. Eur Endocrinol. 2013;9(1):40-7.
11. Numani D, Scarsi C, Ducharme MP. Levothyroxine soft capsules demonstrate bioequivalent pharmacokinetic exposure with the European reference tablets in healthy volunteers under fasting conditions. Int J Clin Pharmacol Ther. 2016;54(2):135-43.
12. Hostalek U, Uhl W, Wolna P, Kahaly GJ. New levothyroxine formulation meeting 95-105% specification over the whole shelf-life: results from two pharmacokinetic trials. Curr Med Res Opin. 2017;33(2):169-74.
13. Lipp HP, Hostalek U. A new formulation of levothyroxine engineered to meet new specification standards. Curr Med Res Opin. 2019;35(1):147-50.
14. Concordet D, Gandia P, Montastruc JL, Mélou A, Lees P, Ferran A, et al. Levothyrox® New and Old Formulations: Are they Switchable for Millions of Patients? Clin Pharmacokinet. 2019;58(7):827-33.
15. Concordet D, Gandia P, Montastruc JL, Mélou A, Lees P, Ferran AA, et al. Why Were More Than 200 Subjects Required to Demonstrate the Bioequivalence of a New Formulation of Levothyroxine with an Old One? Clin Pharmacokinet. 2020;59(1):1-5.
16. Yu LX, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann DJ, et al. Novel bioequivalence approach for narrow therapeutic index drugs. Clin Pharmacol Ther. 2015;97(3):286-91.

Cite this article as: Biswas SA, Tripathi AP, Roy DS. Assessment of the pharmacokinetics, safety, and tolerability of levothyroxine sodium in healthy Indian volunteers. Int J Basic Clin Pharmacol 2022;11:373-7.