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Research Article

ORAL RELATIVE BIOAVAILABILITY OF A ONCE-WEEKLY FORMULATION OF LEVOTHYROXINE SODIUM TO A ONCE-DAILY MARKETED FORMULATION: A RANDOMIZED, CROSSOVER STUDY

Mayuresh D. Utpat,* Dr Rajaram S. Samant, Santoshi B. Kadam and Dr. Prashant J. Palkar

Medical Servvices Department, Akumentis Healthcare Ltd., 204, 5th Floor, G-Corp Tech Park, Kasarvadavali, Near Hypercity, Ghodbunder Road, Thane (West), Maharashtra- 400615, India

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A B S T R A C T

Background: Daily levothyroxine (1.6 mcg/kg/day) is recommended by current guidelines for hypothyroidism. However, difficulty in following stringent administration guidelines affects patient compliance. To tackle this problem, weekly administration of seven times the daily dose is being considered. The current study assesses the relative bioavailability of a once weekly formulation of levothyroxine sodium to a once daily formulation.
Methods: This was an open-label, balanced, randomized, two-treatment, two-sequence, two-period, two-way crossover oral relative bioavailability study. A total of 24 healthy male human subjects were divided into two groups of 12 each and randomized to either weekly or daily treatment with levothyroxine in first period, which were switched between groups in second period after a washout period of 35 days. C_{max} and $AUC_{0\text{-}168h}$ were calculated as primary pharmacokinetic parameters for T4 and T3. **Results:** Ratios of least square means of C_{max} and $AUC_{0\text{-}168h}$ of both formulations for T_4 were 105.35% (95% CI-101.32-109.54%) and 108.65% (104.68-112.78%). For T_3, the ratios of C_{max} and $AUC_{0\text{-}168h}$ were 103.83% (101.47-106.26%) and 103.11% (99.4-106.96%) respectively. All the ratios fell within the accepted bioequivalence limit of 80-125%. **Conclusion:** Weekly levothyroxine formulation was found to be bioequivalent with daily treatment. Thus, the formulation can be used as an alternative to daily thyroid replacement therapy.

INTRODUCTION

Hypothyroidism is the most common thyroid disorder, more commonly found in women, and becomes frequent with age [1]. Prolonged hypothyroidism may lead to a rare, but serious complication, myxedema coma. Hypothyroid patients usually need lifelong treatment [2]. Current guidelines recommend daily levothyroxine therapy (with a dose of 1.6 mcg/kg/day) [3]. This can achieve euthyroidism, but patient compliance is a problem, mainly due to inconvenience caused by stringent administration guidelines. The daily dose has to be taken in a fasting state and any meal is to be consumed after 30 minutes of the dose. Moreover, any drugs known to interfere with its absorption are to be taken 4 hours apart from dosing. Inconvenience caused by these guidelines often renders the patients non-compliant with the therapy. Weekly administration of thyroxine is being considered to tackle this problem, wherein a collective dose seven times that of daily dose is administered at once every week. Thus, the patients will have to follow the stringent guidelines only once in a week.

Corresponding author:* **Mayuresh D. Utpat
Medical Servvices Department, Akumentis Healthcare Ltd., 204, 5th Floor, G-Corp Tech Park, Kasarvadavali, Near Hypercity, Ghodbunder Road, Thane (West), Maharashtra- 400615, India

This strategy is hoped to help improve patient compliance, and therefore, outcomes from the therapy. The present study is aimed to assess bioequivalence of a once-weekly levothyroxine formulation against a once-daily formulation.

SUBJECTS AND METHODS

The study was conducted in accordance with IEC-approved protocol and clinical research guidelines established by basic principles defined in ICH-GCP guidelines, Schedule Y (as amended) of Central Drugs Standard Control Organization (CDSCO) 2005, Ethical Guidelines for Biomedical Research on Human Participants, ICMR (Indian Council of Medical Research; 2006), Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), ICH (Step 5) 'Guidance on Good Clinical Practices', OECD principles of Good Laboratory Practice and all other applicable regulatory requirements. Informed consent and protocol (RH/2017/07/07) were reviewed and approved as per aforementioned guidelines before the commencement of the study.

Subjects

Total 24 healthy, adult male human subjects with normal BMI and weight not less than 50 kg were enrolled for the study. Subjects in normal health as determined by personal medical history and clinical examinations including vital signs and laboratory examinations, non-alcoholics and non-smokers,

without prior history of drug abuse, and willing to adhere to protocol and provide written informed consent were included in this study.

Subjects with major illness at or 90 days before screening, history or presence of drug abuse/alcoholism/smoking, tobacco/gutkha/pan masala consumption, or abnormal diet patterns during four weeks preceding the screening had to be excluded.

Study Drug

Euthyroid Tablets containing Levothyroxine Sodium, USP 700 mcg, marketed by Akumentis Healthcare Ltd (Batch no. UHT17039, Manufacturing Date: May-2017, Expiry Date: Oct-2018) were used as test product (T).

Thyronorm Tablets containing Levothyroxine Sodium, USP 100 mcg, marketed by Abbott Ltd (Batch no. AEC0396, Manufacturing date: February 2017, Expiry date: January 2019) were used as reference product (R).

Study Design and Drug Administration

This was an open-label, balanced, randomized, two-treatment, two-sequence, two-period, two-way crossover oral relative bioavailability study. Although this study followed open-label design, analysts were kept blind to the sequence of administration of treatments. The subjects found to be suitable for the study against the inclusion and exclusion criteria were randomized to the treatments using PROC PLAN code of SAS® (SAS Institute Inc., USA) version 9.4. Total duration of the study was 50 days. After an overnight fast of at least 10 hours, Euthyroid tablets or Thyronorm tablets were administered as per randomization while in a sitting position with approximately 240 ml of water at ambient temperature. In period-1, participants assigned to test product were administered Euthyroid tablet for one day under fasting condition. Participants assigned to reference product were administered Thyronorm tablets for seven days under fasting condition. Following a washout period of 35 days, the treatments were switched between the groups during period-2. All the subjects were monitored under direct supervision of principal investigator for compliance with the therapy. Pre-dose blood samples were collected 30 minutes, 15 minutes and five minutes before dosing. Further samples were collected at every half an hour interval for first 3 hours; 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 18 hours and 24 hours for the remainder of the first day and once every day for next six days. Primary pharmacokinetic parameters were C_{max} (maximum observed serum drug concentration) and $AUC_{0\text{-}168hr}$ (area under serum concentration-time curve measured to the 168-hour concentration using Linear Trapezoidal rule). T_{max} (Time for attaining C_{max}) was the secondary pharmacokinetic parameter. All these parameters were calculated from serum concentration of T_4 (levothyroxine) estimated by liquid chromatography/tandem mass spectrometry (LC-MS-MS) (AB Sciex API 2000™ LC-MS-MS system). Percentage relative bioavailability was calculated as follows:

$$\frac{\text{Geometric mean of } AUC0_{0\text{-}168h\,(T)}}{\text{Geometric mean of } AUC0_{0\text{-}168h(R)}} \times \frac{Dose_R}{Dose_T} \times 100$$

Statistical Analysis

Descriptive statistics (geometric mean, arithmetic mean, median, standard deviation, coefficient of variation, minimum, and maximum) were computed and reported for primary and secondary pharmacokinetic parameters. All the statistics were computed by SAS® (SAS Institute Inc., USA) version 9.4 and were compared for test and reference treatments. Bioequivalence was evaluated by means of statistical analysis of variance (ANOVA) with 95% confidence intervals (CI) of the test/reference ratio with logarithm-transformed data. The bioequivalence acceptance criteria required that the 95% CI should be contained within the acceptance interval of 80-125%.

***Safety Assessment*:** All 24 subjects were included in safety assessment. Safety assessment was based on clinical laboratory evaluation, chest X-ray (P/A view), ECG recordings, clinical examination and vital signs (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate) measurement and post-study clinical laboratory safety evaluation. Laboratory assessments (haematology, biochemistry, serology and urine analysis), chest X-ray (P/A view) and ECG recordings were done at the time of screening. Clinical examination and measurement of vital signs (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate) were recorded prior to check-in and check-out of each period and prior to dosing in each period. Sitting blood pressure and radial pulse rate were measured and recorded at 1.00, 3.00 and 5.00 hours after each dosing (within ± 40 minutes of the scheduled time, referring to the last recording) in each period. Subjects were questioned for well-being at the time of clinical examination and recording of vital signs. A safety blood sample was collected for post-study safety assessment (haematology and biochemistry) from all dosed subjects at the end of the study.

RESULTS

All 24 subjects completed the study and all 24 were included in safety analysis. Demographic profile is shown in table-1.

The C_{max} and $AUC_{0\text{-}168hr}$ for T_4 are shown in table-2. The Geometric least square mean C_{max} for test product was 76.51 ng/mL compared to 80.61 ng/mL of reference product. $AUC_{0\text{-}168}$ for test product was 4075.15 ng.hr/mL compared to 3750.63 ng.hr/mL of reference product. The statistical analysis revealed that the ratios of these pharmacokinetic parameters (95% confidence interval) were within the bioequivalence criteria of 80-125%; $C_{max(T)}/C_{max(R)}$= 105.35% (95% CI- 101.32-109.54%), $AUC_{0\text{-}168hr(T)}/AUC_{0\text{-}168hr(S)}$= 108.65% (104.68-112.78%).

Linear plot of mean serum concentration of T_4 after administration of test product (T) and reference product (R) (N=24) is shown in figure-1.The C_{max} and $AUC_{0\text{-}168hr}$ for T_3 (tri-iodothyronine) are shown in table-3. The geometric least square mean C_{max} for test product was 144.84 ng/mL compared to 139.49 ng/mL of reference product. $AUC_{0\text{-}168}$ for test product was 13179.7 ng.hr/mL compared to 12782.52 ng.hr/mL of reference product. The ratios of these pharmacokinetic parameters were within the bioequivalence criteria of 80-125%; $C_{max\ (T)}/C_{max(R)}$ = 103.83% (101.47-106.26), $AUC_{0\text{-}168hr\,(T)}/AUC_{0\text{-}168hr(R)}$ = 103.11 (99.4-106.96).

Linear plot of mean serum concentration of T_3 after administration of test product (T) and reference product (R)

(N=24) is shown in figure-2. No severe, serious or life-threatening adverse events were reported throughout the study. A total of seven adverse events were reported in seven out of 24 subjects; three during period-1 and four during period-2. Out of seven, six adverse events were possibly related to the study drug; two in the test group and four in the reference group. One adverse event reported in reference group was unlikely to be related to the study drug.

In the test group, most commonly reported adverse event was headache (two subjects, 8.33%). In the reference group, most commonly reported adverse events were headache (two subjects, 8.33%) and nausea (two subjects, 8.33%). All the adverse events were mild in intensity. All the subjects were followed up till resolution of adverse events.

Table 1 Demographic Data of Subjects

Variable	Profile	Percentage
Race	Asian	100%
Gender	Male	100%
Diet	Vegetarian	16.67%
	Non-vegetarian	83.33%
Smoking status	Non-smokers	100%
Alcohol consumption	Non-alcoholics	100%
	Mean	**SD**
Age (yr)	31	5.5
Height (cm)	168	4.79
Weight (kg)	62.2	6.96
Body-mass index (BMI) (kg/m^2)	22.03	2.11

Table 2 C_{max} and $AUC_{0\text{-}168hr}$ of Thyroxine (T_4)

Pharmacokinetic parameter	Test product (T)	Reference product (R)	T/R (%)	95% CI
C_{max} [a] (ng/mL)	76.516	80.606	105.35	101.32-109.54
$AUC_{0\text{-}168hr}$ [b] (ng.hr/mL)	4075.145	3750.632	108.65	104.68-112.78

[a]C_{max}: Peak plasma concentration; [b]$AUC_{0\text{-}168\ hr}$: Area under plasma concentration-time curve from 0 hr to 168 hr

Table 3 C_{max} and $AUC_{0\text{-}168hr}$ of Tri-iodothyronine (T_3)

Pharmacokinetic parameter	Test product (T)	Reference product (R)	T/R (%)	95% CI
C_{max} [a] (ng/mL)	144.843	139.494	103.83	101.47-106.26
$AUC_{0\text{-}168hr}$ [b] (ng.hr/mL)	13179.7	12782.521	103.11	99.4-106.96

[a]C_{max}: Peak plasma concentration; [b]$AUC_{0\text{-}168\ hr}$: Area under plasma concentration-time curve from 0 hr to 168 hr

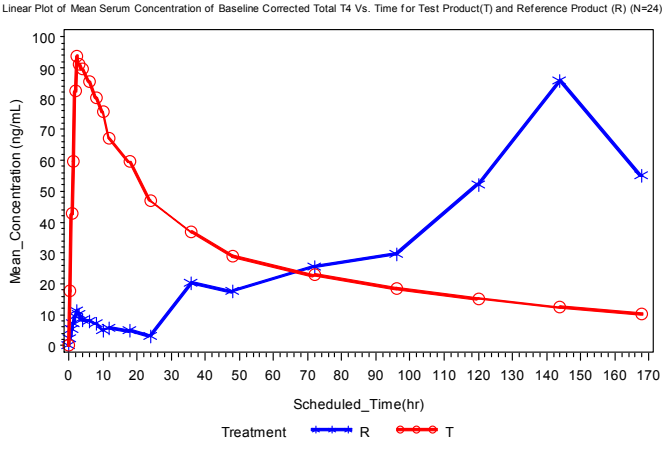

Figure 1 Linear plot of mean serum concentration of baseline corrected total T_4 vs. time for test product (T) and reference product (R) (N=24)

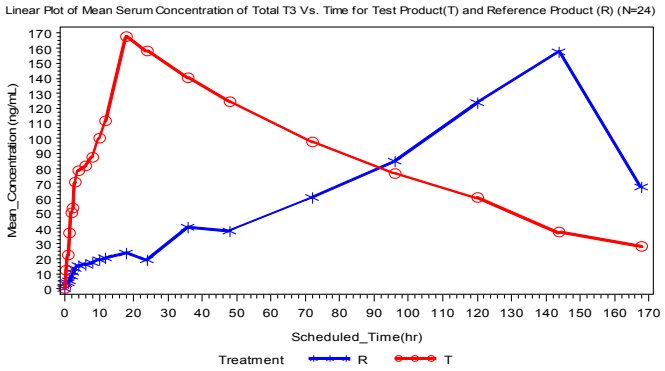

Figure 2 Linear plot of mean serum concentration of baseline corrected total T_3 vs. time for test product (T) and reference product (R) (N=24)

DISCUSSION

In patients with chronic disorders, non-compliance is a recognized problem. Dosing frequency, treatment duration, number of medications are some reasons behind non-compliance [4]. In case of thyroid replacement therapy, stringent administration guidelines for daily administration of thyroxine [1] often lead to non-compliance [5]. In a study, it was found that 82% of patients were non-compliant to daily replacement therapy with levothyroxine [6]. According to the administration guidelines, levothyroxine has to be consumed in fasting state and any meal should be taken about 30 minutes after its administration [1]. Also, it is to be administered at least four hours apart from that of any other medication interfering with its absorption [7]. Difficulty in following the stringent guidelines often leads to non-compliance, and as a result, patients remain hypothyroid despite high doses of levothyroxine for daily therapy.

It is proven that the half life of levothyroxine is seven days, but its biological effects may last longer [8]. T_4, a pro-hormone, gets converted to active form tri-iodothyronine (T_3). The process of this conversion is auto-regulated [8]. Taking this into account, weekly thyroxine administration seems plausible and could be used to increase patient compliance so that better results are achieved. Some studies have evaluated the efficacy of weekly levothyroxine therapy. *Grebe et al* [8] assessed the efficacy of weekly regimen against daily regimen and found that the weekly regimen was well-tolerated and tissue markers of thyroid hormones were similar between two study groups. *Wasoori et al* [9] found the once weekly administration of thyroxine to be safe and effective in non-compliant patients with no signs of hyperthyroidism. Another study by *Rajput et al* [10] reported similar findings. *Bornschein et al* [1] reported higher free T_4 and similar total T_3 in patients undergoing daily LT_4 treatment who were euthyroid from a randomized, single-blind, crossover study. Various case studies report thyroxine absorption test to detect pseudo-malabsorption followed by once weekly thyroxine to achieve euthyroidism [11, 12]. Similar findings were reported by a clinical study by *Walker et al* [13] in patients failing to achieve euthyroidism despite daily dose of thyroxine. After thyroxine absorption test followed by weekly dose of thyroxine for 4 weeks, serum TSH levels significantly decreased. These findings from different studies and case reports suggest that once weekly administration of thyroxine is efficacious and safe

where hyperthyroidism symptoms are unlikely to occur, and can be useful in patients non-compliant with the therapy.
The main objective of the study was to assess the relative bioavailability of Euthyroid tablets containing levothyroxine sodium, 700 mcg with reference product, Thyronorm tablets containing levothyroxine sodium, 100 mcg in healthy, adult human male subjects and to monitor safety in the subjects.

In this study, 24 male subjects were divided into two groups of 12 each and a crossover design was followed; so that each subject served as his own control. According to the USFDA & EMA Guidance, in studies to determine bioequivalence after a single dose, the ratio of the C_{max} and AUC for test and reference products should be contained within the acceptance interval of 80-125%. As seen in table-2 and table-3, the ratios of least square means of C_{max} and AUC_{0-168h} fell within the acceptance interval of 80-125%. This indicated that the two formulations were bioequivalent.

In this study, the weekly levothyroxine formulation was found to be bioequivalent with daily treatment as per pharmacokinetic parameters. Oral weekly levothyroxine was well-tolerated with no indication of acute treatment toxicity compared to daily therapy. These results suggest that once weekly thyroxine replacement therapy is safe and arguably efficacious.

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Conflicts of Interest: Authors declare no conflicts of interest.

Authors' Contribution:

M.U.: Analysis and interpretation of data; statistical analysis; Drafting of manuscript
R.S.: Statistical analysis; Drafting of Manuscript
S.K.: Statistical analysis; Drafting of Manuscript
P.P.: Statistical analysis; Drafting of Manuscript

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