

Clinical Efficacy and Pharmacokinetics of Levothyroxine Suppository in Patients with Hypothyroidism

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This study aimed to elucidate the clinical efficacy and pharmacokinetics of levothyroxine (LT4) suppository, thus, we examined the pharmacokinetics of thyroxine (T4) after the administration of the suppository in thyroidectomized rats and examined dose and the levels of free T4 (FT4) in patients with hypothyroidism receiving suppositories. Thyroidectomized rats were administered with LT4 solution and LT4 suppository (30 µg/kg), and plasma T4 concentrations were measured using LC/MS. The AUC_{0-168} of T4 after rectal administration of the LT4 suppository was 64% lower than these values after oral administration. To evaluate clinical effect of LT4 suppository, we enrolled 6 Japanese patients with hypothyroidism (2 men and 4 women; age, 68.2±13.5 years) who were administered LT4 suppository at Kameda Medical Center from 2007 to 2013 in this case series. The FT4 level during the administration of suppositories was significantly lower than that during the administration of tablets (0.657±0.183 ng/dL vs. 1.25±0.51 ng/dL, $p=0.034$). The FT4/dose ratio for the suppository was significantly 44% lower than that for the tablet ($p=0.020$). In conclusion, although the bioavailability of LT4 is lower after administration of the suppository than after the oral formulation, it was suggested that T4 levels can be maintained in patients with hypothyroidism by administering LT4 suppositories at a dose 1.8 times higher than that of the tablet. Thus, the administration of LT4 suppository can be an alternative for treatment with oral medication in clinical practice.

Key words levothyroxine; suppository; clinical efficacy; pharmacokinetics; hypothyroidism

Thyroid hormones are important hormones that regulate protein synthesis and energy metabolism in the body; the thyroid hormone thyroxine (T4) consists of four molecules of iodine and triiodothyronine (T3) consists of three molecules of iodine. The major thyroid hormone synthesized in the thyroid gland is T4. T4 is converted to T3 in the liver and kidneys by removal of 1 of the 4 molecules of iodine.

A disease associated with the deficiency of these thyroid hormones is known as hypothyroidism, and patients with this disease have low levels of free T3 (FT3) and free T4 (FT4) and high levels of thyroid-stimulating hormone (TSH). In 90% or more patients, hypothyroidism is caused by chronic autoimmune (Hashimoto's) thyroiditis, which is caused by cell- and antibody-mediated destruction of the thyroid tissue.¹⁾ Thyroidectomy, radioiodine treatment, and external radiation therapy are well-known causes of hypothyroidism. Furthermore, hypothyroidism is much more common in women than in men, and a majority of patients with hypothyroidism develop goiter.²⁾ The results of the United States National Health and Nutrition Examination Survey indicated that the incidence of hypothyroidism was 4.6% (0.3% overt and 4.3% subclinical), and the prevalence of hypothyroidism was higher in subjects in the old age groups and in Caucasian and Hispanic subjects.³⁾

Synthetic levothyroxine (LT4) is widely used for the treatment of hypothyroidism. LT4 mimics the normal physiology of the thyroid gland, which mostly secretes T4 as a prohormone. The average bioavailability of LT4 is about 80%, and because the plasma half-life of LT4 is long (7 d), once-daily

treatment achieves nearly constant serum T4 and T3 levels.⁴⁾ Almost all patients with hypothyroidism are treated orally with LT4. However, if patients receiving chronic administration of LT4 undergo surgery and are unable to take oral medication for several days, LT4 should be administered intravenously. Although some injectable formulations of LT4 are available in Europe and the United States, such formulations are not available in Japan.

Rectal administration using suppositories is an alternative for patients in whom administration *via* the oral route is not feasible. Compared to intravenous administration, rectal administration is advantageous in that no aseptic handling is required and the patients can self-administer the drugs at home. Thus, rectal administration of LT4 suppository seems to be clinically useful for the treatment of patients with hypothyroidism in whom oral administration is not possible. However, few studies have reported the clinical efficacy of rectal administration of LT4,⁵⁾ and little is known about the pharmacokinetics of T4 after rectal administration.

This study aimed to elucidate the clinical efficacy and pharmacokinetics of LT4 suppository. We evaluated the pharmacokinetics of T4 after administration of LT4 suppository in thyroidectomized rats and compared it with that after oral administration. Furthermore, we examined the dose of LT4 and the levels of FT4, FT3, and TSH in patients with hypothyroidism treated with LT4 tablets and suppositories.

MATERIALS AND METHODS

Materials Levothyroxine sodium of Japanese Pharma-

The authors declare no conflict of interest.

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copeia grade was kindly donated by Sandoz K.K. (Tokyo, Japan), and reagent-grade levothyroxine sodium was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). LT4 tablets were purchased from Aska Pharmaceutical Co., Ltd. (Thyradin-S tablet, Tokyo, Japan) and Sandoz K.K. (Levothyroxine sodium tablet [Sandoz]). Hard fats Witepsol H-15 and Witepsol E-75 (Vosco, Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) were used as suppository bases. All other chemicals were of reagent grade.

Preparation of LT4 Suppository The LT4 suppository was prepared using the fusion method. Briefly, LT4 tablets were ground and mixed well with melted suppository bases, Witepsol H-15 and Witepsol E-75 (1:1). Then, the resulting mixture was poured into a plastic tube (ϕ , 5 mm) for rectal administration in rats and into plastic molds (75 μ g of LT4/1.35 g of suppository) for patients with hypothyroidism. The suppository was allowed to cool at room temperature and stored at 4°C until use.

Animals and Thyroidectomy Four- to six-week-old male Sprague-Dawley rats (Japan SLC Inc., Shizuoka) were housed with free access to normal diet (CE-2; Crea Japan, Tokyo) and water and were maintained on a 12-h light/12-h dark cycle in a room with controlled temperature and humidity. The study was performed in accordance with guidelines of Experimental Animal Ethics Committee of the University of Shizuoka.

The rats were anesthetized with pentobarbital (40 mg/kg, intraperitoneally). The thyroid glands of the rats were resected from the tracheal tube. At 2 to 4 weeks after the surgery, blood samples were collected from the jugular vein of the thyroidectomized rats, and concentrations of T4 and TSH in the plasma were measured using LC/MS and enzyme-linked immunosorbent assay (ELISA) (Rodent TSH ELISA Test Kit; Endocrine Technologies Inc., Newark, CA, U.S.A.). Rats with plasma T4 and TSH concentrations less than 20 ng/mL and more than 15 ng/mL, respectively, after thyroidectomy were used in the pharmacokinetics study.

Pharmacokinetics of T4 after Oral and Rectal Administration in Thyroidectomized Rats Thyroidectomized rats were orally administered with LT4 (30 μ g/kg) dissolved in water. For rectal administration, the rats were treated with LT4 suppository (30 μ g/kg) under light anesthesia with ethyl ether, and then ligated the anal of rats until 10 h after the administration. Blood samples were collected from the jugular vein before and at 1, 3, 6, 10, 24, 48, 72, and 168 h after the administration of LT4 solution and suppository. Plasma samples were isolated from the whole blood by centrifugation and stored at -20°C until the determination of the concentration of T4.

Determination of T4 in the Plasma of Rats The plasma concentration of T4 was determined using LC/MS. Briefly, 50 μ L of pindolol (100 ng/mL) as an internal standard 0.1% of formic acid (500 μ L) was added to the plasma sample of rats (50 μ L). After centrifugation at 3000 rpm for 10 min, the supernatant fluid was applied to a solid-phase extraction plate (Oasis HLB 96-well μ Elution Plate; Waters, Milford, MA, U.S.A.). The elute (10 μ L) was injected in the chromatographic system for analysis. LC was performed using the analytical column (Symmetry C₁₈; 5 μ m, 2.1 mm \times 150 mm, Waters) with mobile phase (0.1% formic acid/acetonitrile=60/40) delivered at flow rate of 0.2 mL/min. The mass spectrometer (Micro-mass ZQ; Waters) was operated in positive ion mode at m/z

777 for T4 and m/z 249 for pindolol. The limit of quantitation was 1 ng/mL, and the intra-assay coefficient of variation was less than 7.0%.

Clinical Effect of Levothyroxine Suppository in Patients with Hypothyroidism We enrolled six Japanese patients with hypothyroidism who were administered LT4 suppository at Kameda Medical Center from 2007 to 2013 in this case series. They were treated with oral thyroid hormone replacement therapy by using LT4 tablets. Five patients had undergone surgery for thyroid cancer (4 patients) and esophageal cancer (1 patient). Discontinuation of a nasogastric tube because of an unexpected trouble was found in 1 patient. Then, the ingestion of food and the oral administration of tablets were limited, and thus administration of the LT4 suppository instead of the tablet was initiated. Daily dose of LT4 of tablet and suppository in each patient were selected by the physician according to clinical requirements.

Daily dose of LT4 and serum levels of FT4, FT3, and TSH during the administration of LT4 tablet and LT4 suppository were analyzed from the medical records of each patient. Data during the period of administration of the suppository were obtained from 6 to 14 d after the day on which the treatment was switched from tablet to suppository, when the FT4 level was expected to reach the steady-state, and data during the period of administration of the tablet were obtained at the nearest day on which the tablet was changed to the suppository. All patients or their family gave written informed consent, and the study protocol was approved by the Ethics Committee of Kameda Medical Center.

Data Analysis Pharmacokinetic parameters of the change of plasma T4 concentrations from the value of before the administration (base line) were calculated by non-compartmental analysis in rats. The linear trapezoidal method was used to calculate the area under the plasma concentration-time curve from 0 to 168 h (AUC_{0-168}) after the oral and rectal administration in rats. The peak plasma concentration (C_{max}) and time to C_{max} (T_{max}) were obtained by inspection.

All data are represented as the mean and standard deviation (S.D.). GraphPad Prism software (version 5.0; GraphPad, San Diego, CA, U.S.A.) was used for all statistical analysis. Student's *t*-test and paired *t*-test were used to assess the differences of pharmacokinetic parameters in rats and clinical data in patients with hypothyroidism, respectively. A *p* value of <0.05 was considered statistically significant.

RESULTS

Pharmacokinetics of T4 after Oral and Rectal Administration in Thyroidectomized Rats

Table 1. Pharmacokinetic Parameters of the Change in the Plasma Thyroxine (T4) Concentration from the Baseline after Oral and Rectal Administration of Levothyroxine (LT4) in Thyroidectomized Rats

Pharmacokinetic parameters	Oral administration	Rectal administration
T_{max} (h)	19.3 \pm 7.2	14.8 \pm 8.6
C_{max} (ng/mL)	52.6 \pm 28.1	15.3 \pm 7.9*
AUC_{0-168} (ng \cdot h/mL)	2023 \pm 1473	719 \pm 557

Parameters are expressed as the mean and standard deviation (S.D.) in 5 to 6 rats. T_{max} , time to the peak plasma concentration; C_{max} , the peak plasma concentration; AUC_{0-168} , the area under the plasma concentration-time curve from 0 to 168 h.

* Significant difference (*p* < 0.05) compared to the value in oral administration.

trations of T4 were 59.9 ± 5.4 ng/mL in 4- to 6-week-old rats. Thyroidectomy significantly decreased the plasma concentration of T4, and 2 to 4 weeks after the thyroidectomy, the T4 concentrations were 7.48 ± 5.57 and 8.11 ± 8.06 ng/mL in rats receiving oral and rectal administration of LT4, respectively. Unlike the plasma concentration of T4, the plasma TSH level in thyroidectomized rats was significantly higher than that in rats before the surgery (22.6 ± 1.2 vs. 1.30 ± 0.32 ng/mL).

The plasma concentration of T4 reached maximum at 24 h after the oral administration of LT4 in thyroidectomized rats, whereas the maximum plasma concentration of T4 was achieved at 10 h after rectal administration of LT4 suppository

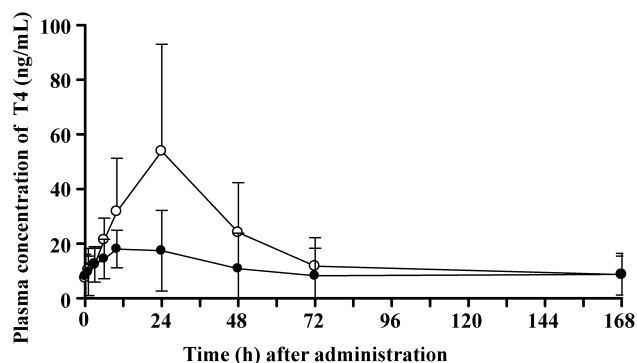


Fig. 1. Plasma Concentrations of Thyroxine (T4) after Oral (○) and Rectal (●) Administration of Levothyroxine (LT4) in Thyroidectomized Rats

Each point represents the mean and standard deviation (S.D.) of 5 to 6 rats.

(Fig. 1). The plasma concentration of T4 returned to the baseline level after 168 and 72 h after the oral and rectal administration, respectively. Time courses of changes in the plasma concentration of T4 from the baselines, the values before the administrations, were similar to those course as the original concentrations of T4.

We calculated the change in the plasma T4 concentrations of thyroidectomized rats from the baseline (Table 1). The C_{\max} and AUC_{0-168} of T4 after rectal administration of the LT4 suppository was 71% and 64% lower than these values after oral administration, respectively. Relative bioavailability of rectal administration to oral administration from each AUC_{0-168} value was calculated at 34%.

Clinical Effect of Levothyroxine Suppository in Patients with Hypothyroidism We enrolled six Japanese patients (2 men and 4 women; age, 68.2 ± 13.5 years) with hypothyroidism who were administered LT4 suppository in this case series (Table 2). Daily dose of LT4 was 117 ± 54 μ g for tablets and 161 ± 89 μ g for suppositories, and dose of suppository was 1.43-fold higher than that of the tablet ($p=0.033$). All patients experienced no adverse events, and the administrations of tablets and suppositories were well tolerated.

The serum levels of FT4, FT3, and TSH in patients with hypothyroidism after treatment with LT4 tablets and suppositories are shown in Fig. 2. The FT4 level during the administration of suppositories was significantly lower than that during the administration of tablets (0.657 ± 0.183 ng/dL vs. 1.25 ± 0.51 ng/dL, $p=0.034$). Similarly, the FT3 level significantly decreased after the treatment was changed from

Table 2. Demographics of Patients with Hypothyroidism Enrolled in This Study and the Dose of Levothyroxine (LT4) Tablets and Suppositories

Patients No.	Gender	Age	Height (cm)	Body weight (kg)	LT4 dose (μ g)	
					Tablet	Suppository
1	M	54	169	51	75	113
2	M	61	173	n.d.	150	225
3	F	80	n.d.	n.d.	200	300
4	F	73	154	53.8	50	50
5	F	86	148	45.8	100	150
6	F	55	165	56	125	125
Mean		68.2	162	51.7	117	161*
S.D.		13.5	10	4.4	54	89

n.d., not determined. Data of the height and body weight in patients 2 and 3 were not available because they were not able to stand up for the measurements of these data.

*Significant difference ($p<0.05$) compared to the value of LT4 tablet.

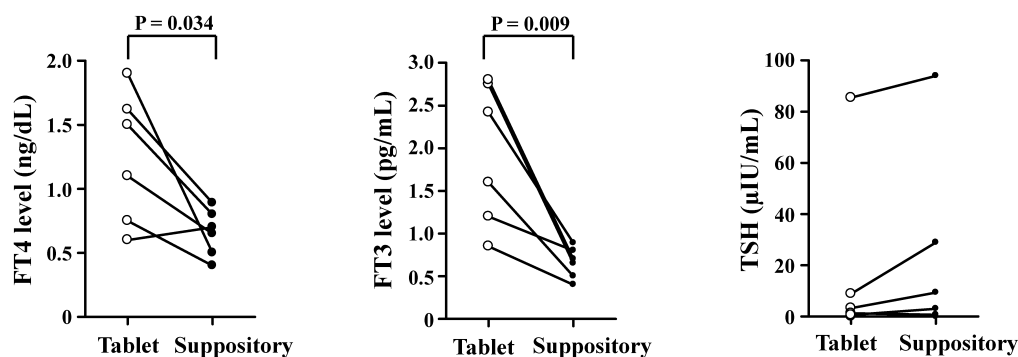


Fig. 2. Serum Free Thyroxine (FT4), Free Triiodothyronine (FT3), and Thyroid Stimulating Hormone (TSH) Levels of Patients with Hypothyroidism during the Period of Treatment with Levothyroxine (LT4) Tablets and Suppositories

Each point indicates individual values.

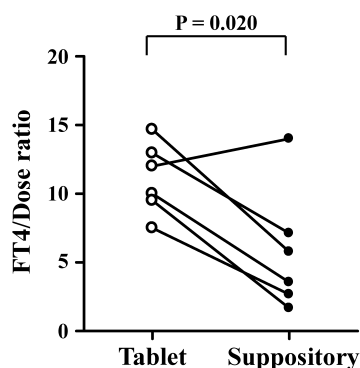


Fig. 3. The Free Thyroxine (FT4)/Dose Ratio for Levothyroxine (LT4) Tablets and Suppositories in Patients with Hypothyroidism

Each point indicates individual value.

tablet to suppository (1.94 ± 0.83 pg/mL vs. 0.657 ± 0.183 pg/mL, respectively, $p=0.009$). The TSH levels during the administration of the tablet and suppository were 16.6 ± 33.9 and 22.7 ± 36.6 μ IU/mL, respectively, and no significant difference was observed in these levels. The FT4/dose ratio for the suppository was significantly ($p=0.020$) 44% lower than that for the tablet (Fig. 3).

DISCUSSION

This study aimed to elucidate the clinical efficacy and pharmacokinetics of LT4 suppository; thus, we examined the pharmacokinetics of T4 after the administration of the suppository in thyroidectomized rats and examined the levels of FT4, FT3, and TSH in patients with hypothyroidism receiving suppositories.

The mean FT4 level in the patients with hypothyroidism was 0.66 ng/dL during treatment with the suppository. Given that the therapeutic target for FT4 levels generally ranges from 0.8 to 1.8 ng/dL, suppositories might not be optimal to achieve the target levels of FT4. On the other hand, the FT4 level during treatment with LT4 tablets was 1.3 ng/mL. In this study, the LT4 doses of tablet and suppository were selected according to the dosage that appeared to be clinically required. Consequently, the dose varied in each patient and among the patients. To compare the clinical efficacy between the tablet and the suppository, the ratios between FT4 levels and dose were calculated. The FT4/dose ratio for the suppository was 56% of that for the tablet. This result suggests that the dose of the LT4 suppository should be 1.8 times higher than that of the tablet.

To date, only one case report has described the clinical application of LT4 sodium suppositories.⁵⁾ Similarly, a suppository prepared from the powder formulation of dried thyroid maintains the serum TSH level to the target level during treatment with LT4 tablet, but the dose of the suppository is approximately twice as high as the dosage for oral administration using an LT4 tablet.⁶⁾ In addition, the serum T4 levels in rabbits treated with thiamazole increased after the administration of LT4 suppository and the AUC of T4 was dose dependent.⁷⁾ Thus, we have suggested that LT4 suppositories at a dose twice that of LT4 tablets can be used in patients with hypothyroidism who are unable to consume oral medications.

To clarify the pharmacokinetics of LT4 suppositories, we determined the time-course of plasma concentrations of T4 after administration of LT4 to thyroidectomized rats *via* rectal

and oral routes. T4 levels decreased after removal of the thyroid glands, and these levels decreased to 10–15 ng/mL after 2 weeks. This level was one-fifth of or lesser than the level before the removal of the thyroid gland (approximately, 50 ng/mL); the rats appeared to be an appropriate animal model for hypothyroidism. If the pharmacokinetic study of LT4 is performed in normal rats, the pharmacokinetic data are a combination of endogenous and exogenous T4 levels. The plasma T4 concentration is sufficiently low in thyroidectomized rats owing to depletion of endogenous T4. Therefore, the differences in the plasma T4 concentrations before (baseline) and after administration may have been attributable to the LT4 administered.

When LT4 was administered to the thyroidectomized rats *via* the rectal route, plasma T4 levels remained lower than those after oral administration, and the relative bioavailability, which is a ratio between the AUC obtained after oral administration and AUC obtained after rectal administration, was 34%. This value is similar to the FT4/dose ratio for the suppository that was 56% of the ratio for the tablet. Thus, the bioavailability of LT4 suppository in humans was also lower than that of the tablet, which suggests that the clinical efficacy of the suppository would be lower than that of the tablet. The mechanism of drug absorption from the rectum is probably not different from that in the upper part of the gastrointestinal tract.^{8,9)} Depending on the chemical structures of drugs, drugs may cross the rectal wall either by absorption across the transcellular or paracellular route. Several local host factors, including the mucous layer and the variable volume of rectal fluid, may influence absorption in the rectum. Additionally, the hepatic first-pass elimination of high clearance drugs is partly avoided after rectal administration. The bioavailability between the oral and the suppository formulations were reported to vary depending on drugs.⁹⁾ In particular, the pharmaceutical formulation (*e.g.*, the use of surfactants or other additives, particle size of the active ingredient, *etc.*) may play a major role in the rectal absorption. Further development of LT4 suppository in terms of its formulation and preparation will be required to enhance the absorption and consequently the clinical efficacy.

Transporters are involved in the membrane transport of T4.^{10–12)} Organic anion transporting polypeptides (OATP) 1A2, 1B3, and 1C1 are involved in the transport of T3 and T4.¹⁰⁾ Furthermore, a recent study showed that the monocarboxylate transporters (MCT) 8 and 10, which are specific thyroid hormone transporters, transport thyroid hormones.¹¹⁾ However, the extent of contribution of these transporters to T4 absorption from the small intestine or the upper gastrointestinal tract remains to be clarified. The expression levels of many transporters usually expressed in the gastrointestinal tract differ between the small intestine and the rectum, which, in part, may explain the differences between the bioavailability of T4 after oral and rectal administration observed in our study.

In this study, we evaluated the clinical efficacy of LT4 suppository used in patients with hypothyroidism. One limitation of this study was different durations of treatment with the tablet and the suppository. Varying factors such as pathophysiological conditions of patients could not be excluded. Furthermore, because the tablet was switched to the suppository mainly after the patients became unable to take oral medication, their dietary intake may have been different during the

time periods of treatment with the tablet and the suppository. Further prospective studies involving a larger number of patients are required by setting an appropriate control group.

In conclusion, although the bioavailability of LT4 is lower after administration of the suppository than after the oral formulation, it was suggested that T4 levels can be maintained in patients with hypothyroidism by administering LT4 suppositories at a dose 1.8 times higher than that of the tablet. Because the method to prepare the suppository used in this study is simple and does not require any special equipment, the suppository can be prepared in the hospital pharmacy. Thus, the administration of LT4 suppository can be an alternative for treatment with oral medication in clinical practice.

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