SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 505239, 5 pages
doi:10.4061/2011/505239

Clinical Study

Can Levothyroxine Be Taken as Evening Dose? Comparative Evaluation of Morning versus Evening Dose of Levothyroxine in Treatment of Hypothyroidism

Rajesh Rajput,[1] Sumanto Chatterjee,[1] and Meena Rajput[2]

[1] *Department of Medicine VII & Endocrinology, Postgraduate Institute of Medical Sciences, Rohtak, Haryana 124001, India*
[2] *Department of Community Medicine, Post graduate Institute of Medical Sciences, Rohtak, Haryana 124001, India*

Correspondence should be addressed to Rajesh Rajput, rajputrajmeena@hotmail.com

Received 15 March 2011; Revised 27 April 2011; Accepted 12 May 2011

Academic Editor: Julie A. Sosa

152 drug naïve primary hypothyroid patients were divided into morning (Group 1) and evening (Group 2) dosing group and evaluated for change in biochemical profile, physical functioning and Quality of Life during the course of 12 weeks of study. At the end of 12 weeks 70 (90.90%) subjects in Group 1 and 72 (96%) in Group 2 achieved euthyroidism. On evaluation clinical symptoms and total clinical scores improved in both the groups at the end of 6 and 12 weeks. Significant improvement in thyroid profile was seen in both the groups at the end of 6 and 12 weeks (P value <.0001). On intergroup comparison, no significant difference in thyroid profile was seen at 6 and 12 weeks between the morning and the evening dose group. Similar dose of levothyroxine was required to achieve euthyroidism in both the groups. Though an early restoration of euthyroidism was seen in evening group, the difference when compared to the morning group was not statistically significant. On assessment of QoL, statistically significant improvement in various parameters was seen in both the groups. Hence, from the study we inferred that evening dose is as efficacious as morning dose and provides an alternate dosing regimen.

1. Introduction

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. The prevalence of overt hypothyroidism increases with age, with more than 10% of the women of over 60 years having subclinical hypothyroidism [1, 2]. Whether primary or secondary, treatment of choice is Levothyroxine sodium. The primary advantage of Levothyroxine therapy is that the peripheral deiodination mechanism can contribute to produce the amount of T3 required under physiological control. Following oral administration, the absorption of levothyroxine is incomplete and variable, especially when taken with food. The amount absorbed decreases from 80% in the fasting state to 60% in the fed state [3]. Interference with Levothyroxine has been documented with cholestyramine resin, sucralphate, iron sulphate, calcium preparations, aluminum antacids, raloxifene, activated charcoal, various soya products, and food and herbal remedies [4–7]. Also fiber-enriched diet, the traditional Indian diet, has been shown to adversely affect the absorption of Levothyroxine [8]. Intake of coffee in early morning is a social habit in this part of the country, which may interfere with the absorption of levothyroxine [9]. So as convention the drug is given at least half an hour before breakfast, and failure to follow this advice results in variable absorption of levothyroxine sodium. However, many patients with hypothyroidism find it inconvenient to take the drug on an empty stomach in the morning because of their lifestyle, and intake of multiple other drugs which they are regularly consuming and often request their treating physicians to prescribe the drug at some alternate time of the day. The results of the study conducted by Bolk et al. [10] in which they showed a marked improvement in the thyroid hormone profile of twelve patients after switching from morning to the evening dose, prompted us for further investigation. They found it to be safe and well tolerated. They found out that changing the timings of thyroxine ingestion does not affect the circadian rhythm

of TSH and iodothyronine secretion, and hence, testing the thyroid profile of the patients in the morning after ingesting levothyroxine at night bears no significance in the outcome of the study. Keeping these facts in mind, this study was planned to compare the efficacy of morning versus bedtime dose of thyroxine in patients of hypothyroidism.

2. Materials and Methods

The study was conducted with 77 newly diagnosed drug naïve subjects in group 1 and 75 in group 2, who were randomly selected from the patients attending "Endocrinology Clinic" at PGIMS Rohtak. All patients were having Hashimoto's thyroiditis as underlying cause of hypothyroidism. A written consent was taken from all patients. Patients in group 1 were given levothyroxine in the morning minimum half an hour before breakfast, and in group 2 the drug was given minimum 2 hours after dinner. None of the patients used medication known to interfere with levothyroxine absorption, nor were they known to have gastro-intestinal disease. Pregnant and postpartum patients with hypothyroidism were not included in either group. Initial dosage was calculated as 1.6 mcg/kg body weight, and the closest commercially available dosage, that is, 75/100/125 mcg was started. In the event of nonachievement of euthyroidism (defined by normalization of T4 and TSH) at the end of six weeks, the dose was increased by 25 mcg/day. The study was carried for a time period of 12 weeks, and assessment of quality of life (by RAND-(Research and Development) 36 scoring system [11]) and clinical profile (according to the clinical scores given by Billewicz et al. [12]) were done at baseline, two, six and 12 weeks. Biochemical parameters were assessed at baseline (before start of treatment) and at the end of six, and 12 weeks. fT3 (normal range—2.4–4.2 pg/mL) and fT4 (normal range—0.89–1.76 ng/dL) were assessed by chemiluminescent method using analyzer and kits of Siemens (ADIVA Centaur CP). TSH (normal range 0.34–4.25 m IU/L) was done by immunometric assay (PC RIA MAS by Startek) by Turbo TSH [^{125}I] using IRMA kit. Lipid profile was assessed by Konelab 30i using analyzing kits by Randox. Patients were studied on the basis of change in clinical symptoms at presentation, improvement in Quality of life and change in the biochemical parameters with special reference to thyroid function tests and lipid profile. Clinical symptoms were scored according to the scoring system given by Billewicz et al. [12]. Quality of life was assessed by RAND 36 [11] which measured health according to eight subscales which are: physical functioning, role limitation due to physical health, role limitation due to emotional problems, energy/fatigue, emotional wellbeing, social functioning, pain and general health. The scale score ranged from 0 to 100 for every subscale, with a higher outcome meaning a better health status.

3. Statistical Analysis

Primary end point was a change in the thyroid profile of the subjects and achievement of euthyroidism in each group measured at the end of six and 12 weeks. Secondary end points of the study were change in QoL, thyroid symptom score, and lipid profile. For calculation of sample size, results from the pilot study conducted by Bolk et al. was used where it was found that to get a significant difference in TSH of 1 mIU/L in both the groups at the end of study with a power of 80%, 75 subjects should be enrolled in each group. Z test was used to compare the difference in mean of free T3, free T4, and lipid profile between each group at the beginning, six and 12 weeks. Paired t-test was used to assess the intragroup change at six and 12 weeks. The value of TSH in either group did not follow Gaussian data distribution on followup as most of the data were clustered in a narrow range in both the groups at 6 weeks and 12 weeks. Hence, nonparametric tests: Wilcoxon two-sample test was applied for intergroup comparison and Wilcoxon sign-rank test was applied for intragroup comparison. For intergroup comparison of total score of clinical signs and symptoms and QoL, Wilcoxon two-sample test was applied. For intragroup comparison of total score of clinical signs and symptoms and QoL, Wilcoxon sign-rank test was applied. The data collected and analyzed is expressed as mean ± SD.

4. Observations and Results

The mean age of patients in group 1 was 32.84 ± 13.06 years and that in group 2 was 35.76 ± 10.59 years with a mean weight of 60.94 ± 15.58 kg and 62.76 ± 13.15 kg in group 1 and group 2, respectively, at baseline. At the end of 12 weeks the mean weight was 60.21 ± 15.69 and 62.28 ± 13.35 kg in group 1 and 2, respectively. There was no significant difference in body weight between the two groups both at baseline and at the end of 12 weeks (P value = .92 and .92 at baseline and at 12 weeks, resp.). The sex ratio of male : female was 1 : 4.5 in group 1 and 1 : 6.9 in group 2.

In the current study, 101 ± 15.8 mcg of levothyroxine was required in Group 1, and 100.40 ± 13.28 mcg in Group 2 of levothyroxine was required to achieve euthyroidism. There was no statistically significant difference in the amount of drug used in both the groups (P value = .94). It was seen that at the end of 6 weeks, 32 (41.55%) of subjects in Group 1 and 35 (46.66%) of subjects in Group 2 achieved euthyroidism. At the end of 12 weeks, 70 (90.90%) subjects in Group 1 and 72 (96%) in Group 2 achieved euthyroidism. We observed that there was an early restoration of euthyroidism (TSH < 4.25 mIU/L) in the group receiving levothyroxine as evening dose. However, no statistically significant difference was seen at the end of 6 weeks and 12 weeks (P value = .51 and .19). Improvement in thyroid profile (increase in fT3 and fT4 and decrease in TSH) at 6 weeks and 12 weeks was seen both in the morning group as well as in the evening, and it was highly significant in comparison with their baseline thyroid function (P value < .0001). However, on intergroup comparison at the end of 6 and 12 weeks, no significant change in the thyroid profile was seen (P value = .31 in both fT4 and TSH at the end of 12 weeks) (Table 1). No patient in either group had a low serum TSH at either 6 or 12 weeks.

We also analyzed the secondary outcomes of the study in both of the groups. Total serum cholesterol levels decreased significantly in both of the groups at the end of 12 weeks

Table 1: Comparison of biochemical parameters (data expressed as mean ± SD) of Group 1 and Group 2 at the end of 6 and 12 wks.

Biochemical parameter	Group 1			Group 2		
	Baseline	6 wks	12 wks	Baseline	6 wks	12 wks
fT3 (pg/mL)	2.09 ± 1.03	2.91 ± .75 ($P < .0001$)	3.48 ± 1.09 ($P < .0001$)	2.15 ± 1.03	2.93 ± 1.01 ($P < .0001$)	3.20 ± 0.54 ($P < .0001$)
fT4 (ng/dL)	0.72 ± 0.59	1.31 ± 0.45 ($P < .0001$)	1.5 ± 0.33 ($P < .0001$)	0.74 ± 0.5	1.30 ± 0.49 ($P < .0001$)	1.48 ± 0.31 ($P < .0001$)
TSH (mIU/L)	82.79 ± 56.32	17.03 ± 18.33 ($P < .0001$)	5.13 ± 9.36 ($P < .0001$)	78.23 ± 43.15	12.64 ± 44.27 ($P < .0001$)	3.27 ± 4.19 ($P < .0001$)
Triglyceride (mg/dL)	158.50 ± 89.36	141.17 ± 62.4 ($P = .08$)	141.10 ± 62.76 ($P = .08$)	158.75 ± 89.72	149.82 ± 78.07 ($P = .50$)	137.24 ± 68.37 ($P = .09$)
Cholesterol (mg/dL)	194.95 ± 63.21	182.19 ± 44.27 ($P = .48$)	177.66 ± 39.71 ($P = .012$)	196.88 ± 75.69	176.64 ± 38.35 ($P = .029$)	173.85 ± 38.25 ($P = .015$)
HDL (mg/dL)	43.25 ± 20.76	39.88 ± 6 ($P = .14$)	44.36 ± 15.74 ($P = .311$)	42.84 ± 12.91	41.56 ± 12.91 ($P = .54$)	43.29 ± 12.14 ($P = .88$)
LDL (mg/dL)	119.44 ± 48.08	112.88 ± 34.48 ($P = .29$)	108.59 ± 33.45 ($P = .56$)	113.06 ± 40.05	105.79 ± 29.85 ($P = .27$)	103.68 ± 31.27 ($P = .65$)
VLDL (mg/dL)	30.86 ± 17.79	29.19 ± 14.11 ($P = .19$)	28.31 ± 13.13 ($P = .34$)	31.54 ± 15.80	29.20 ± 12.69 ($P = .13$)	27.44 ± 15.33 ($P = .76$)

when compared to their baseline (P value = .01 for both of the groups). However, when Group 1 was compared to Group 2, there was no significant statistical difference. There was a reduction of 8% cholesterol in Group 1 and 11.7% in Group 2. Serum triglyceride levels were reduced by 10.9% in group 1 and 13.5% in group 2. The study also revealed that there was a reduction in LDL in both the groups (9% in group 1 and 8.8% in group 2). However, there was no statistical significant improvement in LDL and serum triglyceride levels when intragroup and intergroup comparison was made (Table 1).

In our study we observed that physical tiredness, followed by mental lethargy, muscle pain, and increase in body weight were the most common symptoms in patients of group 1, whereas periorbital puffiness was the most common sign. Similarly in group 2, physical tiredness was the most common presenting symptom, followed by mental lethargy, muscle pain, and dryness of hair, while slowing of ankle jerk and slow movements were the most common signs observed. Among the male patients, it was seen that in both the groups, physical tiredness was the most common symptom (72% in group 1 and 90% in group 2) whereas periorbital puffiness and slowing of ankle jerk were the most common signs in group 1 and group 2, respectively. The total clinical scores decreased significantly in both the groups (showing improvement) (P value of .0001 and .0005 in group 1 and 2, resp., when compared to their baseline at the end of 12 weeks), but the difference was not statistically significant when the morning group was compared to the evening group (P value = .37 and .31 at the end of 6 and 12 weeks, resp.). Physical tiredness was the most common symptom to be resolved after 12 weeks of therapy, and periorbital puffiness in Group1 and slowness of movement in Group 2 were the most common signs which had maximum improvement after 12 weeks of therapy.

On evaluation of the results of assessment of quality of life by RAND-36 scoring system, it was seen that all the parameters decreased in both the groups. It was noticed that there was a significant improvement in terms of physical functioning and role limitation due to physical health in both the groups at the end of 12 weeks when compared to its baseline. It was also found that there was a significant improvement in the role limitation due to emotional problems in group 2 at the end of 12 weeks when compared to its baseline. No significant results were found in group 1. Improvement in the rest of the parameters was found to be statistically insignificant in both the groups. Scores of social functioning was found to be markedly improved in group 1 when it was compared to that of group 2 at the end of 2, 6, and 12 weeks.

5. Discussion

The present study shows noninferiority of the evening dose of levothyroxine when compared to the morning dose in terms of improvement in signs and symptoms, quality of life, and dosage of the drug required for achievement of euthyroidism. Marked improvement in thyroid profile was seen in both the groups. Improvement in total cholesterol, LDL, and serum triglyceride levels was seen in both the groups, and the difference between the groups was not significant. The results of our study give the patients a choice of timings of their daily intake of drug. In modern day busy world, this may prove boon to millions of people, who due to their busy schedule or intake of other drugs in the morning hours were not able to adhere to the requirements of fasting morning intake of levothyroxine.

The mean dose of levothyroxine required to achieve euthyroidism and the number of patients who achieved euthyroidism at 12 weeks were slightly better in the bedtime

treatment group, although neither of these parameters were significantly different from the morning dose group. We attribute our findings to better availability of the drug at night due to slowness of gastric motility, noninterference with breakfast and circadian rhythm, and activity of deiodinase which might alter the metabolism of the drug in the body [13–16]. Findings of present study are in contrast to the study done by Huynh et al. [17] where they had shown that nonfasting regimen of levothyroxine administration are associated with higher and more variable serum TSH concentrations, and if a specific serum TSH goal is desired, thereby avoiding iatrogenic subclinical thyroid disease, then fasting ingestion ensures that TSH concentration remain within narrowest target range. The noninferiority of nighttime administration of levothyroxine in our study can be explained by the fact that ingesting drug at least two hours after dinner, eating nothing thereafter, and going to the bed provides several hours of empty stomach to the drug in contrast to ingesting breakfast half an hour after morning administration of drug and will result in at least similar if not better bioavailability of drug. Recently Bolk et al. [18] also published the results of their study involving ninety patients where they compared the effects of morning versus evening administration of levothyroxine sodium. This study showed that levothyroxine taken at bedtime significantly improved thyroid hormone levels, but quality of life parameters and plasma lipids showed no significant change as compared to morning intake. These findings strengthens the observation of present study that although bedtime administration of levothyroxine is statically not superior to morning fasting administration, but it is also not inferior to morning administration as far as total dose needed to achieve euthyroidism, number of patients achieving euthyroidism at 12 weeks and with respect to improvement in quality of life parameter and lipid profile. Strength of the present study is the fact that it involves larger number of patients as compared to all previous studies who had no earlier exposure to levothyroxine. Hence, the results of our study are more practical and closer to the real world scenario. Moreover, majority of the patients taking levothyroxine as evening/bedtime dose in the present study find it more convenient and decided to continue with evening/bedtime administration at the end of the study.

An important matter of concern was impact of levothyroxine on circadian rhythm and nocturnal TSH surge when given as evening dose and whether sample for determining thyrotropin levels can be taken in the morning after nighttime administration of levothyroxine. The serum levels of TSH increase in the evening, reach a maximum near sleep onset, and are followed by a progressive decrease during the night and low values during the day [19]. The percentage nocturnal rise of TSH is 71 ± 40% in healthy controls and is maintained in euthyroid patients on levothyroxine therapy taken in the morning (63 ± 51%) and patients with mild hypothyroidism (54 ± 33%), whereas in overt hypothyroidism, this nocturnal surge disappears [20]. Bolk et al. [10] in their pilot study found no change in the circadian rhythm of TSH when switching the time of levothyroxine ingestion to bedtime. There was no significant change in T4, rT3, albumin, and TBG serum levels, or in the T3/rT3 ratio. The relative amplitude and time of the nocturnal TSH surge remained intact. Moreover, Persani et al. [21] showed that bioactivity of TSH has a circadian variation with less bioactive and differently glycosylated TSH molecules secreted during night. These findings bear important practical consequences in our study as the timings for blood sampling for monitoring thyroid hormones can still be done in the morning as per present norm even if the patient is taking levothyroxine as evening dose.

Our data do not allow us to conclude that ingestion of levothyroxine 2 hours after the evening meal provides a sufficiently long interval to avoid the interfering effects of food on levothyroxine absorption. Although subjects were instructed to take their levothyroxine at least 2 hours after dinner, we did not collect data on the exact interval between dinner and levothyroxine ingestion in the bedtime-dosing subjects, and thus, we do not know if the average meal-dose interval was closer to 2, 3, or 4 hours, or longer. Meal-dose intervals of greater than 2 hours may be necessary to assure an empty stomach at the time of levothyroxine ingestion, particularly when the preceding evening meal contained solid and/or fatty foods.

From the study we inferred that there was at least similar bioavailability and metabolism of the drug either given as morning or evening dose. So in a nutshell, we can say that evening dose is as efficacious as morning dose in improvement of thyroid profile, reduction in total cholesterol levels, improvement of clinical signs and symptoms, and improvement in quality of life. In the modern busy life with hectic morning schedule, the results give hope for an alternate dosing regimen.

References

[1] W. M. Wiersinga, "Subclinical hypothyroidism and hyperthyroidism. I. Prevalence and clinical relevance," *Netherlands Journal of Medicine*, vol. 46, no. 4, pp. 197–204, 1995.

[2] M. P. Vanderpump, W. M. Turnbridge, J. M. French et al., "The incidence of thyroid disorders in the community: a twenty year follow up of Whickham survey," *Clinical Endocrinology*, vol. 43, pp. 55–68, 1995.

[3] L. H. Fish, H. L. Schwartz, J. Cavanaugh, M. W. Steffes, J. P. Bantle, and J. H. Oppenheimer, "Replacement dose, metabolism, and bioavailability of Levothyroxine in the treatment of hypothyroidism," *The New England Journal of Medicine*, vol. 316, no. 13, pp. 764–770, 1987.

[4] S. I. Sherman, E. T. Tielens, and P. W. Ladenson, "Sucralfate causes malabsorption of L-thyroxine," *American Journal of Medicine*, vol. 96, no. 6, pp. 531–535, 1994.

[5] N. Singh, P. N. Singh, and J. M. Hershman, "Effect of calcium carbonate on the absorption of levothyroxine," *Journal of the American Medical Association*, vol. 283, no. 21, pp. 2822–2825, 2000.

[6] N. R. Campbell, B. B. Hasinoff, H. Stalts, B. Rao, and N. C. W. Wong, "Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism," *Annals of Internal Medicine*, vol. 117, no. 12, pp. 1010–1013, 1992.

[7] E. S. Siraj, M. K. Gupta, and S. S. Reddy, "Raloxifene causing malabsorption of levothyroxine," *Archives of Internal Medicine*, vol. 163, no. 11, pp. 1367–1370, 2003.

[8] Y. Liel, I. Harman-Boehm, and S. Shany, "Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypo- thyroid patients," *Journal of Clinical Endocrinology & Metabolism*, vol. 81, no. 2, pp. 857–857, 1996.

[9] S. Benvenga, L. Bartolone, M. A. Pappalardo et al., "Altered intestinal absorption of L-thyroxine caused by coffee," *Thyroid*, vol. 18, no. 3, pp. 293–301, 2008.

[10] N. Bolk, T. J. Visser, A. Kalsbeek, R. T. van Domburg, and A. Berghout, "Effects of evening vs morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients," *Clinical Endocrinology*, vol. 66, no. 1, pp. 43–48, 2007.

[11] A. L. Stewart, C. Shebourne, and R. D. Hays, "Summary and discussion of MOS measures," in *Measuring Functioning and Well Being: The Medical Outcome Study Approach*, A. L. Stewart, Ed., pp. 345–371, Durham, NC, USA, Duke University Press, 1992.

[12] W. Z. Billewicz, R. S. Chapman, J. Crooks et al., "Statistical methods applied to the diagnosis of hypothyroidism," *The Quarterly Journal of Medicine*, vol. 38, no. 150, pp. 255–265, 1969.

[13] P. Wilson, G. Perdikis, R. A. Hinder, E. J. Redmond, M. Anselmino, and E. M. Quigley, "Prolonged ambulatory antroduodenal manometry in humans," *American Journal of Gastroenterology*, vol. 89, no. 9, pp. 1489–1495, 1994.

[14] M. T. Hays, "Localization of human thyroxine absorption," *Thyroid*, vol. 1, no. 3, pp. 241–248, 1991.

[15] E. Stone, L. A. Leiter, J. R. Lambert, J. D. Silverberg, K. N. Jeejeebhoy, and G. N. Burrow, "L-thyroxin absorption in patients with short bowel," *Journal of Clinical Endocrinology & Metabolism*, vol. 59, no. 1, pp. 139–141, 1984.

[16] E. S. Keck, C. F. Wolf, and E. F. Pfeiffer, "The influence of circulating thyroxine serum concentration on hepatic thyroxine deiodinating activity in rats," *Experimental and Clinical Endocrinology*, vol. 96, no. 3, pp. 269–277, 1990.

[17] T. G. B. Huynh, B. Nayak, J. Loh, S. Soldin, and J. Jonklaas, "Timing of levothyroxine administration affects serum thyrotropin concentration," *Journal of Clinical Endocrinology & Metabolism*, vol. 94, no. 10, pp. 3905–3912, 2009.

[18] N. Bolk, T. J. Visser, J. Nijman, I. J. Jongste, J. G. P. Tijssen, and A. Berghout, "Effects of evening vs morning levothyroxine intake," *Archives of Internal Medicine*, vol. 170, no. 22, pp. 1996–2003, 2010.

[19] G. Brabant, K. Prank, U. Ranft et al., "Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman," *Journal of Clinical Endocrinology and Metabolism*, vol. 70, no. 2, pp. 403–409, 1990.

[20] R. Adriaanse, J. A. Romijn, E. Endert, and W. M. Wiersinga, "The nocturnal thyroid-stimulating hormone surge is absent in overt, present in mild primary and equivocal in central hypothyroidism," *Acta Endocrinologica*, vol. 126, no. 3, pp. 206–212, 1992.

[21] L. Persani, M. Terzolo, C. Asteria, F. Orlandi, A. Angeli, and P. Beck-Peccoz, "Circadian variations of thyrotropin bioactivity in normal subjects and patients with primary hypothyroidism," *Journal of Clinical Endocrinology and Metabolism*, vol. 80, no. 9, pp. 2722–2728, 1995.