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Original Article

THE PHARMACOKINETICS OF 2 DOSES (50 µG AND 100 µG) LEVOTHYROXINE TREATMENT IN ATHYREOTIC PATIENTS

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ABSTRACT

Objective: Hypothyroid has still be a problem in Thailand. Lack of pharmacokinetics information of levothyroxine in athyreotic patients for modify dosing. Therefore, the aim of this study was to investigate the pharmacokinetic parameters of 2 doses of levothyroxine (50 µg and 100 µg) in such group of patients.

Methods: The 24 athyreotic patients were recruited and randomly assigned to receive 50 µg or 100 µg of levothyroxine. The pharmacokinetic parameters (C_{max}, T_{max}, AUC_{0-8}, k_e, $T_{1/2}$ and V_d) of FT4 and TSH were calculated by the non-compartment model. The parameters of 2 doses were compared.

Results: From the results found that, by monitoring FT4, there was no statistically significant difference ($p>0.05$) of almost all pharmacokinetic parameters between 2 doses except C_{max} which has significant greater in 100 µg of levothyroxine. While all pharmacokinetics parameters of TSH were not statistically significant difference. The use of non-compartment model seems appropriate for calculation of pharmacokinetic parameters of FT4 ($R^2 = 0.81$) while it has poor predictive capacity in terms of TSH ($R^2 = 0.24$).

Conclusion: In conclusion, administration of 50 µg and 100 µg of levothyroxine to athyreotic patients have similar pharmacokinetic in term of FT4 (non-significant different in Tmax, AUC) and TSH. Further study of these parameters in more subjects is needed.

Keywords: Pharmacokinetics, Athyreotic patients, Levothyroxine

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INTRODUCTION

Hypothyroid is the condition that mostly found in athyreotic patients. The incidence of low free T4 (FT_4) and high Thyroid Stimulating Hormone (TSH) is about 0.3% while the incidence of low thyroid hormone is found to 4.3% [1-3] The general treatment of hypothyroid should gradually modified drug dosing. American Association of Clinical Endocrinologists recommended Levothyroxine (L-T4) 1.6 mcg/kg/day by begin with 12.5 mcg/day and then increase dose gradually depends on age, weight, cardiovascular status and duration of hypothyroid [4-5].

In Thailand, the endocrine specialist recommended high dose oral levothyroxine 1000 µg for a single dose. Currently, there have not been studied of efficacy and side effects of high doses regimen.

However, there are several studies in high doses of levothyroxine in patients with hypothyroid [6-7], the study found that myxedema coma or myxedema ileus, Levothyroxine oral route has variable absorption, but patients had a better response after administration. Intravenous levothyroxine can make a higher level of thyroid hormone. However, it cannot conclude that, which appropriate dose should be administered in severe hypothyroidism.

Vicky Blakesley *et al.*[8]reported Bioequivalence of Levothyroxine oral 400, 450 and 600 µg in healthy volunteer and measured thyroid hormone to determine C_{max} (maximum serum concentration), time to $C_{max,}$ and AUC (area under the serum concentration-time curve) and suggested that the bioequivalence study of levothyroxine should use endogenous T4 in the calculation, and the serious adverse effects were not found in high-dose levothyroxine. In Thailand, there is a lack of pharmacokinetic information of levothyroxine pharmacokinetics in hypothyroid patients. Therefore, this study aimed to investigate the pharmacokinetic parameters of 2 doses levothyroxine in such patients.

MATERIALS AND METHODS

Patients

Twenty-four primary hypothyroidism patients with underlying well-differentiated thyroid cancer were recruited. Patients had a Total or Near-total thyroidectomy and stop levothyroxine for 6 w and had ^{131}I radiation therapy which is available as standard treatment.

Inclusion criteria

1. Males or females whose ages between 15-60 y old
2. TSH>30mIU/ml
3. No underlying diseases such as Cardiovascular diseases, Liver insufficiency (AST and/or ALT>3 times UL), renal insufficiency (Scr>1.5 mg/dL)
4. No receiving other drugs that affect levothyroxine absorption such as calcium-containing drugs, anticonvulsants, oestrogens, and proton pump inhibitors or H2 blockers.

Exclusion criteria

Patients were excluded if they

1. Were poor compliance with drug regimens
2. Were pregnancy or lactation
3. Had hypersensitivity or intolerate to thyroxine
4. Had infectious or liver diseases
5. Were considered by the physician as inappropriate to be included in this study.

Drug administration

Patients were administered levothyroxine 50 µg (50µg) 1 tablets or Levothyroxine 100 µg (50µg 2 tablets) single dose.

Pharmacokinetic study

Pharmacokinetic analysis

Levothyroxine plasma concentrations were analysed as a function of time and the following pharmacokinetic parameters were obtained for each subject; the maximum plasma concentration (Cmax), Area under the concentration versus time curve for 8 h (AUC0-8), Elimination rate constant (ke), and volume of distribution (Vd). All pharmacokinetic parameters of free T4 (FT4) and Thyroid

Stimulation hormone (TSH) were assessed by Win-nonlin professional software (version1, Pharsight corporation, Pato Alta,California) and non-compartment methods were used.

Data analysis

Student t-test statistic was used to test the different of pharmacokinetic parameters between 2 groups of different regimens. The statistically significant difference was considered when p value was less than 0.05.

RESULTS

The pharmacokinetic parameters that found in 24 hypothyroid subjects were presented in table 1 and table 2 respectively

Table 1: Pharmacokinetics parameters of FT4 in 24 hypothyroid subjects

Pharmacokinetic parameters (Mean+SD)	L-thyroxine 50(µg) n=12	L-thyroxine 100(µg) n=12	P value*
Cmax (ng/ml)	0.25+0.06	0.46+0.29	0.027
Tmax (h)**	3+0.4	2.92+0.45	0.83
AUC 0-8 (ng/dL*h)	1.93+1.41	3.18+2.31	0.101
Ke (h^{-1})***	0.03+0.02	0.02+0.01	0.24
CL (mL/min)***	5.72+5.27	5.52+2.34	0.88
T1/2 (h)***	32.14+22.61	39.70+18.72	0.74
Vd (L)***	205.36+76.34	266.0+43.13	0.057

*between Thyroxine group, **n=4 for Thyroxine 100 (µg) n=3 for Thyroxine 50 (µg), ***n=10 for Thyroxine 100 (µg) n=11 for Thyroxine 50 (µg), Average R^2= 0.81

Table 2: Pharmacokinetics parameters of TSH in 24 hypothyroid subjects

Pharmacokinetic parameters (Mean+SD)	L-thyroxine 50(µg) n=12	L-thyroxine 100(µg) n=12	P value*
Cmax (ng/ml)	163.5+114.3	142.14+56.37	0.48
Tmax (h)**	2.3+1.5	4.3+3.3	NA
AUC 0-8 (ng/dL*h)	995.53+405.14	1166.3+764.1	0.42
Ke (h^{-1})***	0.019+0.017	0.02+0.01	0.36
CL (mL/min)***	0.0046+0.003	0.0025+0.035	0.28
T1/2 (h)***	107.20+103.94	90.24+118.52	0.74
Vd (L)***	0.406+0.23	1.015+0.869	0.057

*between Thyroxine group, **n=10 for Thyroxine 100 (µg) n=11 for Thyroxine 50 (µg), ***n=9 for Thyroxine 100 (µg) n=11 for Thyroxine 50 (µg), Average R^2= 0.24

DISCUSSION

According to the results, the pharmacokinetic parameters of levothyroxine 50 µg and 100 µg which measure by monitor FT4 have not significant difference except peak concentration (Cmax) is higher in levothyroxine 100 µg, while all pharmacokinetic parameters in terms of TSH were not significant difference. It seems that may be the pharmacokinetic of levothyroxine may have non-linear behaviour.

When comparison of these parameters with the previous study found that, the t_{max} and average half-life were similar to this study.[9-11] The much variations is C_{max} and AUC when compare to previous studies since due to the hypothyroid status of patients in this study which may had lower T4 baseline and 50-100 µg single dose cannot make FT4 reach for normal range and it implied that non-compartmental method could be used in calculation of pharmacokinetic parameters of LT4 with good R^2 (average = 0.8), while is not appropriate use for TSH because R^2 is quite low (average =0.2). Moreover, the sensitivity of TSH is less than FT4.

This study leads to persuaded establishing the use of the pharmacokinetic model for monitoring FT4 in athreotic patients which is useful in levothyroxine dose adjustment.

However, this study had some limitations, because of a small number of subjects, the pharmacokinetics parameters may be not generalised for every patient, further study with more number of subjects are needed. The second point is there is no repeated study for application of this model to another group of patients for proving about the accuracy of the model. Using this model for levothyroxine dose adjustment in another group of athyreotic patients for measuring the accuracy may help to prove about the generalization of this proposed model.

CONCLUSION

In conclusion, administration of levothyroxine (50 µg) and levothyroxine (100 µg) have similar pharmacokinetic in term of FT4 (non-significant different in Tmax, AUC) and TSH. Further study of these parameters in more subjects is needed.

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CONFLICT OF INTERESTS

Declare none

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