

Topic: SIMULATION OF THYROID HORMONE REPLACEMENT

Title: Levothyroxine bioequivalence and hormone replacement studies via feedback control simulations.

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SUMMARY

Background: FDA guidance for testing bioequivalence of levothyroxine (L-T₄) preparations has been challenged by several groups, based on multiple issues. The efficacy of single *versus* combined hormone therapy is also receiving additional scrutiny.

Study: The authors developed a new nonlinear feedback system simulation model of whole-body regulation mechanisms involving dynamics of T₃, T₄, TSH, plasma protein binding, extravascular regulatory enzyme systems, and the hypothalamic-pituitary-thyroid axis, all quantified from human data. To address bioequivalence, the authors explored how to best account for varying and unmeasured endogenous T₄ following dosing with exogenous L-T₄ in euthyroid volunteers in pharmacokinetic (PK) studies, by simulating various dosing scenarios and developing a new and simple correction method. They computed and assessed dosing error effects and baseline corrections using simulator-predicted endogenous T₄ level variations, and compared these with approximate corrections computed directly from PK data.

Results: Simulated replacement after thyroidectomy required 141 µg L-T₄ only to normalize T₃ tissue levels and 162 µg L-T₄ to normalize plasma T₃ levels. A combined dose of approximately 103 µg L-T₄ plus approximately 6 µg T₃ (i.e. a ratio of 18:1) was needed to normalize both plasma T₃ and T₄ and average T₃ tissue levels. However, simulated average tissue T₃ levels were normalized with standard L-T₄-only therapy, and plasma T₃ levels were still within the normal range.

Conclusion: Current standard L-T₄-only treatment is supported for routine replacement needs.

COMMENT

The group of Jo DiStefano is well known for their remarkable, elegant (and often complicated, as it is the case herein) metabolic and pharmacokinetic studies of thyroid hormones. There has been much speculation lately concerning the bioequivalence of thyroid hormone preparations (a problem that not yet exists in our country, but may well appear soon with the generics). Also, several recent articles have dealt with the well-being effects of small changes in thyroxine dosage in hypothyroid patients, as well as

with the additional benefit of adding small doses of L-T₃ to standard L-T₄ therapy. In brief, these studies have shown that minor modifications of the L-T₄ dosage did not affect well-being (Walsh, JCEM 2006) and that addition of L-T₃ was not warranted in the vast majority of patients (Grozinsky-Glasberg, JCEM 2006).

In the present study, 33 volunteers received an oral dose of 400, 450 and 600 µg of L-T₄ and were submitted to sophisticated pharmacokinetic studies, assuming a mean 88% absorption rate. The most important

result of these simulation studies was that a replacement dose of 162 μg of L-T₄ after thyroidectomy was needed (and sufficient) to return plasma T₃ levels to prethyroidectomy values and 141 μg was needed to normalize tissue T₃ levels for full replacement. The 'ideal' physiological dose regimen would be a ratio of 10:1 between L-T₄ and L-T₃. In the present study, a ratio of 18.1 was evidenced, and

average simulated tissue T₃ level was normalized with standard L-T₄-alone therapy. These results are concordant with clinical observations indicating that patients receiving levothyroxine have serum T₃ levels within the normal range. This may be interpreted as supporting current standard replacement therapy with L-T₄ alone.

(Daniel Glinoe, M.D.; Ph.D.)

See Figure below

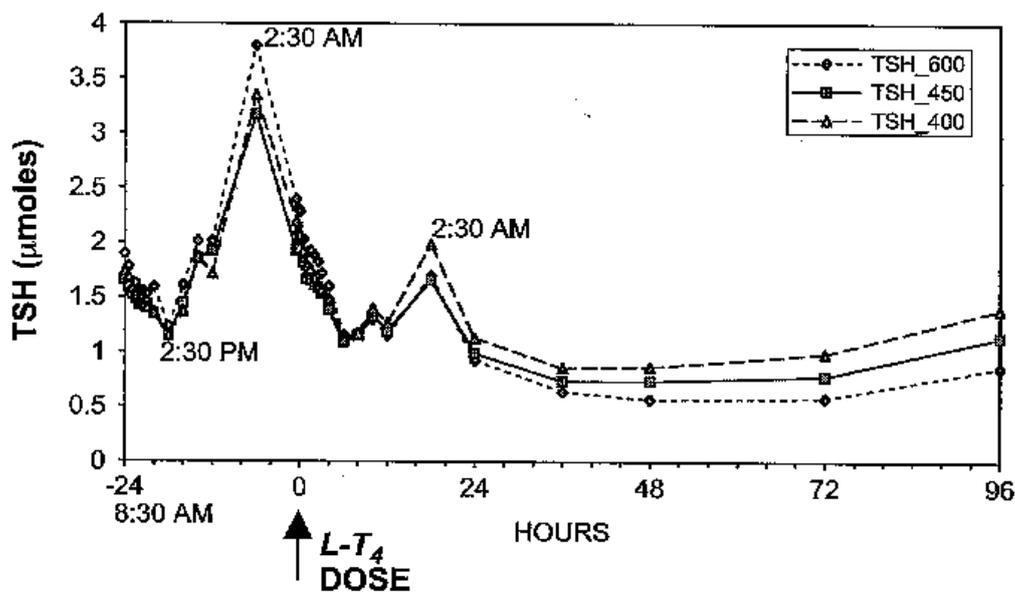


FIG. 4. The three mean $TSH_p(t)$ data sets, from plasma samples collected over 96 hours following 400-, 450-, and 600- μg oral L-T₄ doses in pharmacokinetic (PK) studies by Blakesley *et al.* (5). These were used as inputs for closed-loop parameter estimation, with all data fitted simultaneously, as described in the text and Figure 6. Resulting parameter estimates are given in Table 1.