Simulation of Post-Thyroidectomy Treatment Alternatives for Triiodothyronine or Thyroxine Replacement in Pediatric Thyroid Cancer Patients

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Background: As in adults, thyroidectomy in pediatric patients with differentiated thyroid cancer is often followed by ^{131}I remnant ablation. A standard protocol is to give normalizing oral thyroxine (T_4) or triiodothyronine (T_3) after surgery and then withdraw it for 2 to 6 weeks. Thyroid remnants or metastases are treated most effectively when serum thyrotropin (TSH) is high, but prolonged withdrawals should be avoided to minimize hypothyroid morbidity.

Methods: A published feedback control system model of adult human thyroid hormone regulation was modified for children using pediatric T_4 kinetic data. The child model was developed from data for patients ranging from 3 to 9 years old. We simulated a range of T_4 and T_3 replacement protocols for children, exploring alternative regimens for minimizing the withdrawal period, while maintaining normal or suppressed TSH during replacement. The results are presented with the intent of providing a quantitative basis to guide further studies of pediatric treatment options. Replacement was simulated for up to 3 weeks post-thyroidectomy, followed by various withdrawal periods. T_4 vs. T_3 replacement, remnant size, dose size, and dose frequency were tested for effects on the time for TSH to reach 25 mU/L (withdrawal period).

Results: For both T_3 and T_4 replacement, higher doses were associated with longer withdrawal periods. T_3 replacement yielded shorter withdrawal periods than T_4 replacement (up to 3.5 days versus 7–10 days). Higher than normal serum T_3 concentrations were required to normalize or suppress TSH during T_3 monotherapy, but not T_4 monotherapy. Larger remnant sizes resulted in longer withdrawal periods if T_4 replacement was used, but had little effect for T_3 replacement.

Conclusions: T_3 replacement yielded withdrawal periods about half those for T_4 replacement. Higher than normal hormone levels under T_3 monotherapy can be partially alleviated by more frequent, smaller doses (e.g., twice a day). LT_4 may be the preferred option for most children, given the convenience of single daily dosing and familiarity of pediatric endocrinologists with its administration. Remnant effects on withdrawal period highlight the importance of minimizing remnant size.

Introduction

THYROIDECTOMY IS THE PRIMARY TREATMENT for differentiated thyroid cancer (1–3), and ^{131}I therapy is recommended for patients at risk for disease progression (4). For most patients, chronic thyroxine (T_4) replacement is titrated to maintain a suppressed serum thyrotropin (TSH) (usually ≤ 0.1 mU/L) (5). This TSH suppression is designed to minimize the stimulation of residual thyroid cancer cells, and it is only briefly interrupted when hyperthyrotropinemia is required for radioiodine administration or stimulated thyroglobulin measurements.

After thyroidectomy, patients are usually given synthetic T_4 and/or triiodothyronine (T_3) as initial replacement during their postoperative recovery (the replacement period in Fig. 1) (6). Then, to prepare for ^{131}I administration, patients begin a low iodine diet (1,7,8) and thyroid hormone (TH) is withdrawn to achieve the hyperthyrotropinemia required to stimulate radioiodine uptake into remaining thyroid follicular cells (6,7,9–11). We have recently shown that children with thyroid cancer achieve adequate hyperthyrotropinemia within 14 days of levothyroxine (LT_4) withdrawal, even from a suppressed serum TSH (1, 6). We speculated that this accelerated rise in serum TSH was due to the more rapid T_4

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FIG. 1. Typical thyroid cancer treatment and withdrawal protocol for children. Patients undergo thyroidectomy on day 0, followed by 3 weeks of hormone replacement and 2- to 3-week withdrawal before radioiodine treatment.

clearance and higher TSH to free T_4 ratio observed in children (6) compared with adults.

The goal of the current work was to use feedback control system modeling and computer simulation methodology to predictively explore the impact of different dosing regimens and other patient variables on withdrawal time in children. To quantitatively achieve this objective, a pediatric thyroid system regulation model was developed. Our starting point was an adult dynamic system simulation model of hypothalamic-pituitary-thyroid (HPT) axis regulation (12–15), quantified and validated using a variety of adult human clinical data, spanning a wide range of normal (12,13) to extreme hypothyroid function (12,14). The adult model has been applied in several clinical conditions, including optimization of adult remnant ablation protocols in thyroid cancer (14), criteria for testing bioequivalence of LT_4 preparations (12,15), and central hypothyroidism and circadian rhythm relationships (14). Children have different kinetic parameters governing this control system, with faster hormone metabolism and more pronounced dynamic responses to feedback system perturbations (6). The adult model was modified to account for differences in parameters representing these dynamic processes.

Methods

Pediatric model development

The pediatric thyroid regulation system model (Fig. 2) is structured like the adult HPT-axis model, with a TH secretion,

distribution and elimination (D&E) submodel (bottom), and a brain submodel (top) (12–15). All pediatric model equations and optimized parameter estimates are given in Tables 1 and 2.

TH D&E submodel modifications. The basic six-compartment D&E model structure consists of three compartments for T_4 and three for T_3 , representing fast and slow tissue compartments, as well as free plasma hormone concentrations, as illustrated in Fig. 2, bottom. To reflect the faster pediatric T_4 clearance rates, all five T_4 distribution parameters (k_{12} , k_{21}^{free} , k_{13} , k_{31}^{free} , and k_{02}) were fitted to data (Fig. 3) from a previously published ^{131}I -labeled T_4 tracer kinetic study performed on euthyroid institutionalized children ages 3 to 9 years (17).

For fitting the model to the tracer data, we assumed linearity of the tracer experiment, as we did in developing the original TH D&E model in Fig. 2 (12), and thus used a linearized model to fit the five model parameters k_{12} , k_{21}^{free} , k_{13} , k_{31}^{free} , and k_{02} . The optimizer (weighted extended least squares) in SAAM II modeling software (18) was used for parameter estimation and parameter variability estimation. SAAM II also was used for all simulation studies, with these new parameter values updating the fully quantified nonlinear model. The subject children in reference (17) were about one fourth the size of adults, and scaling for size differences yields a V_p (plasma volume) estimate of ~ 1 L (19).

Brain submodel modifications. The brain submodel replicates hypothalamic and pituitary regulation of TSH secretion in response to plasma T_{3P} and T_{4P} feedback signals, as well as distribution and elimination of TSH in plasma (13). The TSH secretion rate (SR_{TSH}) includes both basal and circadian components, each regulated by T_3 in the brain, denoted globally as T_{3B} . A one-compartment model, quantified by TSH half-life, models TSH D&E well (12).

The adult model includes a “lag” function, f_{LAG} , which represents the combined effects of type-3 deiodinase (D3) down-regulation and “exhausted” pituitary TSH secretion in extreme hypothyroidism (14). This function switches from normal D3 degradation to down-regulated D3 degradation as T_{3B} levels in the brain fall. Because pediatric TH levels tend to

FIG. 2. Pediatric hypothalamic-pituitary-thyroid (HPT) axis model, with pediatric modifications shaded. The adult model (14) was updated for pediatric thyroid hormone (TH) regulatory differences, including faster pediatric thyroxine (T_4) clearance, altered free T_4 to thyrotropin (TSH) ratio, and smaller distribution volumes.

TABLE 1. PEDIATRIC MODEL EQUATIONS

<i>Brain-pituitary submodel equations (14)</i>	
$SR_{TSH}(t) = \left[B_0 + A_0 f_{CIRC} \sin\left(\frac{2\pi}{24}t - \phi_{phase}\right) \right] e^{-T_{3B}^{LAG}(t)}$	TSH secretion rate ($\mu\text{mol/h}$)
$\dot{T}_{SHp}(t) = SR_{TSH}(t) - f_{deg}^{TSH} T_{SHp}(t)$	DE for plasma TSH ($\mu\text{mol/h}$)
$\dot{T}_{3B}(t) = \frac{f_4}{T_{4P}} T_{4P}(t) + \frac{k_3}{T_{3P}} T_{3B}(t) - k_{deg}^{T_{3B}} T_{3B}(t)$	DE for T ₃ in the brain ($\mu\text{mol/h}$)
$\dot{T}_{3B}^{LAG}(t) = f_{LAG} [T_{3B}(t) - T_{3B}^{LAG}(t)]$	DE for lagged T ₃ in the brain ($\mu\text{mol/h}$)
$f_{deg}^{TSH} = 0.53 + \frac{V_{max}^{TSH}}{K_{SH}^{TSH} + T_{SHp}(t)}$	Nonlinear TSH degradation rate function (h^{-1})
$f_{LAG} \equiv k_{LAG}^{HYPO} + \frac{2T_{3B}^{11}(t)}{K_{LAG}^{11} + T_{3B}^{11}(t)}$	Nonlinear lag time function for T _{3B} (t) (h^{-1})
$f_4 \equiv k_3 + \frac{5k_3}{1 + e^{2T_{3B}(t)-7}}$	Nonlinear rate function for T ₄ transport and T ₄ →T ₃ conversion in brain (h^{-1})
$f_{CIRC} \equiv 1 + \left[\frac{A_{max}}{A_0 e^{-T_{3B}^{LAG}(t)}} - 1 \right] \left[\frac{1}{1 + e^{10T_{3B}^{LAG}(t)-55}} \right]$	Circadian rhythm saturation function (h^{-1}) $f_{CIRC} \approx 1$ for eu- and mild hyperthyroidism
<i>Thyroid secretion and D&E submodel equations (13)</i>	
$SR_3(t) = S_3 T_{SHp}(t - \tau) \quad SR_4(t) = S_4 T_{SHp}(t - \tau)$	TH secretion rates ($\mu\text{mol/h}$) with time delay τ
$\dot{T}_{4P}(t) \equiv \dot{q}_1(t) = SR_4(t) + k_{12}q_2(t) + k_{13}q_3(t) - (k_{31}^{free} + k_{21}^{free})FT_{4P}(t) + k_4^{absorb}T_4^{GUT}(t)$	DE for plasma T ₄ ($\mu\text{mol/h}$)
$\dot{q}_2(t) = k_{21}^{free}FT_{4P}(t) - \left[k_{12} + k_{02} + \frac{V_{max}^{D1fast}}{K_m^{D1fast} + q_2(t)} \right] q_2(t)$	DE for fast tissue T ₄ ($\mu\text{mol/h}$)
$\dot{q}_3(t) = k_{31}^{free}FT_{4P}(t) - \left[k_{13} + \frac{V_{max}^{D1slow}}{K_m^{D1slow} + q_3(t)} + \frac{V_{max}^{D2slow}}{K_m^{D2slow} + q_3(t)} \right] q_3(t)$	DE for slow tissue T ₄ ($\mu\text{mol/h}$)
$\dot{T}_{3P}(t) \equiv \dot{q}_4(t) = SR_3(t) + k_{45}q_5(t) + k_{46}q_6(t) - (k_{64}^{free} + k_{54}^{free})FT_{3P}(t) + k_3^{absorb}T_3^{GUT}(t)$	DE for plasma T ₃ ($\mu\text{mol/h}$)
$\dot{q}_5(t) = k_{54}^{free}FT_{3P}(t) + \frac{V_{max}^{D1fast}q_2(t)}{K_m^{D1fast} + q_2(t)} - (k_{45} + k_{05})q_5(t)$	DE for fast tissue T ₃ ($\mu\text{mol/h}$)
$\dot{q}_6(t) = k_{64}^{free}FT_{3P}(t) + \frac{V_{max}^{D1slow}q_3(t)}{K_m^{D1slow} + q_3(t)} + \frac{V_{max}^{D2slow}q_3(t)}{K_m^{D2slow} + q_3(t)} - (k_{46})q_6(t)$	DE for slow tissue T ₃ ($\mu\text{mol/h}$)
$FT_{3P}(t) = [a + bT_{4P}(t) + cT_{4P}^2(t) + dT_{4P}^3(t)]T_{3P}(t)$	Plasma free T ₃ (μmol)
$FT_{4P}(t) = [A + BT_{4P}(t) + CT_{4P}^2(t) + DT_{4P}^3(t)]T_{4P}(t)$	Plasma free T ₄ (μmol)
<i>Two-compartment gut input submodels (13,16)</i>	
$\dot{T}_4^{PILL}(t) = -k_4^{dissolve}T_4^{PILL}(t), \quad T_4^{PILL}(0) = LT_4 \text{ Dose}$	DE for LT ₄ pill dissolution in gut ($\mu\text{mol/h}$)
$\dot{T}_4^{GUT}(t) = k_4^{dissolve}T_4^{PILL}(t) - (k_4^{excrete} + k_4^{absorb})T_4^{GUT}(t)$	DE for absorbable LT ₄ in gut ($\mu\text{mol/h}$)
$\dot{T}_3^{PILL}(t) = -k_3^{dissolve}T_3^{PILL}(t), \quad T_3^{PILL}(0) = LT_3 \text{ Dose}$	DE for LT ₃ pill dissolution in gut ($\mu\text{mol/h}$)
$\dot{T}_3^{GUT}(t) = k_3^{dissolve}T_3^{PILL}(t) - (k_3^{excrete} + k_3^{absorb})T_3^{GUT}(t)$	DE for absorbable LT ₃ in gut ($\mu\text{mol/h}$)
<i>Measurement equations</i>	
$y_{T_{4P}}(t) = 777 T_{4P}(t)/10V_P$	Plasma T ₄ concentration ($\mu\text{g/dL}$)
$y_{T_{3P}}(t) = 651 T_{3P}(t)/V_P$	Plasma T ₃ concentration ($\mu\text{g/L} = \text{ng/mL}$)
$y_{T_{SHp}}(t) = 5.6 T_{SHp}(t)/V_{TSH}$	Plasma TSH concentration (mU/L)

TSH, thyrotropin; DE, differential equation; T₃, triiodothyronine; T₄, thyroxine; TH, thyroid hormone.

be slightly higher than adult levels (19), we adjusted the lag function to down-regulate D3 at slightly higher values of T_{3B} for the onset of pediatric hypothyroidism (see Table 1). TSH distribution volume V_D^{TSH} also was adjusted, to match simulated normal daytime TSH with measured TSH levels in 4- to 6-year-old children (1.6 mU/L) (19), yielding $V_D^{TSH} = 2.5 \text{ L}$.

Quantified model validation. We simulated the quantified model and compared predicted hormone output signals with several sets of clinical data not used in model development.

These included the serum TSH/free T₄ (FT₄) ratio, which is higher in children than adults (20) and the average steady state values of T₃ and T₄ in children ages 4–8 years (19). We also compared simulation results to two clinical radioiodine ablation protocols post-thyroidectomy (6). In the first, clinicians found patients had elevated TSH levels >25 mU/L 7 days after stopping normal replacement dosing. In the second, if patients were given a larger daily LT₄ dose to suppress TSH <0.1 mU/L during replacement, the withdrawal time to TSH levels >25 mU/L was 12.3 ± 0.7 days.

TABLE 2. PARAMETER ESTIMATES, UNITS, UNCERTAINTIES, NOMENCLATURE, AND SOURCES FOR THE PEDIATRIC HYPOTHALAMIC-PITUITARY-THYROID AXIS MODEL

Parameter ^a	Units	Estimate $\pm$ %CV ^b	Definition & Source ^c
$K_{deg}^{T_{3B}}$	h^{-1}	$0.037 \pm 12.6\%$	Degradation rate constant for brain T_3 [$T_{3B}(t)$] (13)
ϕ_{phase}	h	$-3.71 \pm 1.04\%$	Phase constant such that TSH circadian rhythms peak at ~ 2 a.m. (13)
A_0	$\mu\text{mol}/h$	$581 \pm 61.4\%$	TSH circadian amplitude scaling parameter (13)
B_0	$\mu\text{mol}/h$	$1166 \pm 60.7\%$	Maximal TSH basal secretion rate (13)
$k_3 = k_4$	$\mu\text{mol}/h$	$0.118 \pm 6.43\%$	Influx rate of plasma T_3 to TSH-regulatory brain areas (13)
K_m^{D1fast}	μmol	2.85	D1 enzyme Michaelis–Menten constant in fast tissue compartment (13)
K_m^{D1slow}	μmol	95	D1 enzyme Michaelis–Menten constant in slow tissue compartment (13)
K_m^{D2slow}	μmol	0.075	D2 enzyme Michaelis–Menten constant in slow tissue compartment (13)
V_{max}^{D1fast}	$\mu\text{mol}/h$	$3.85 \times 10^{-4} \pm 30.6\%$	D1 enzyme V_{max} in fast tissue compartment (13)
V_{max}^{D1slow}	$\mu\text{mol}/h$	$6.63 \times 10^{-4} \pm 6.27\%$	D1 enzyme V_{max} in slow tissue compartment (13)
V_{max}^{D2slow}	$\mu\text{mol}/h$	$0.00109 \pm 6.27\%$	D2 enzyme V_{max} in slow tissue compartment (13)
S_3	h^{-1}	$3.71 \times 10^{-4} \pm 6.49\%$	T_3 secretion rate constant (13)
S_4	h^{-1}	$0.00168 \pm 7.4\%$	T_4 secretion rate constant (13)
$k_4^{dissolve}$	h^{-1}	1.3	T_4 oral pill dissolution rate constant (13)
$k_4^{excrete}$	h^{-1}	$0.119 \pm 16.3\%$	T_4 excretion rate constant from gut (13)
k_4^{absorb}	h^{-1}	$0.881 \pm 2.2\%$	T_4 absorption rate constant from gut (13)
k_3^{absorb}	h^{-1}	$0.882 \pm 7.2\%$	T_3 absorption rate constant from gut (13)
$k_3^{excrete}$	h^{-1}	$0.118 \pm 7.2\%$	T_3 excretion rate constant from gut (13)
$k_3^{dissolve}$	h^{-1}	$1.78 \pm 32.0\%$	T_3 oral pill dissolution rate constant (13)
A	unitless	0.00289	T_4 plasma protein binding constant (12)
B	mmol^{-1}	0.000214	T_4 plasma protein binding constant (12)
C	mmol^{-2}	0.000128	T_4 plasma protein binding constant (12)
D	mmol^{-3}	-8.83×10^{-6}	T_4 plasma protein binding constant (12)
a	unitless	0.00395	T_3 plasma protein binding constant (12)
b	mmol^{-1}	0.00185	T_3 plasma protein binding constant (12)
c	mmol^{-2}	0.000610	T_3 plasma protein binding constant (12)
d	mmol^{-3}	0.000505	T_3 plasma protein binding constant (12)
k_{05}	h^{-1}	$0.207 \pm 12.8\%$	T_3 D&E degradation rate constant (12)
k_{45}	h^{-1}	$5.37 \pm 16.3\%$	T_3 D&E exchange rate constant (12)
k_{46}	h^{-1}	$0.0689 \pm 4.79\%$	T_3 D&E exchange rate constant (12)
k_{54}^{free}	h^{-1}	2043	Free T_3 D&E exchange rate constant (12)
k_{64}^{free}	h^{-1}	127	Free T_3 D&E exchange rate constant (12)
A_{max}	mmol/h	$2.37 \pm 61.4\%$	Extreme hypothyroid model maximum TSH circadian amplitude; yields a plasma TSH circadian amplitude of ~ 5 mU/L (14)
f_4	h^{-1}	0.118–0.708	Influx and conversion rate constant for plasma T_4 to TSH-regulatory brain areas (14)
k_{degTSH}^{hypo}	h^{-1}	0.53	TSH degradation rate constant in extreme hypothyroidism (14)
k_{LAG}^{hypo}	h^{-1}	$0.0034 \pm 5.87\%$	$T_{3B}(t)$ lag rate constant (14)
k_{50}^{TSH}	mmol	23	TSH D&E Michaelis–Menten constant (14)
V_{max}^{TSH}	mmol/h	6.9	TSH D&E V_{max} constant (14)
V_{TSH}	L	2.5	Pediatric TSH apparent distribution volume (this study, see Methods)
V_p	L	1	Pediatric plasma volume (this study, see Methods)
k_{02}	h^{-1}	$0.0114 \pm 17\%$	T_4 D&E degradation rate (this study, see Methods)
k_{12}	h^{-1}	$0.523 \pm 19.2\%$	T_4 D&E exchange rate constant (this study, see Methods)
k_{13}	h^{-1}	$0.0514 \pm 28.8\%$	T_4 D&E exchange rate constant (this study, see Methods)
k_{21}^{free}	h^{-1}	$2275 \pm 14.4\%$	Free T_4 D&E exchange rate constant (this study, see Methods)
k_{31}^{free}	h^{-1}	$255 \pm 36.0\%$	Free T_4 D&E exchange rate constant (this study, see Methods)
K_{LAG}	unitless	6.5	$T_{3B}(t)$ lag Michaelis–Menten constant (this study, see Methods)
T_{3P}^{EU}	nmol/L	2.6	$T_{3B}(t)$ normalization constant (this study, see Methods; 14)
T_{4P}^{EU}	nmol/L	100.8	$T_{3B}(t)$ normalization constant (this study, see Methods; 14)

^aPediatric model parameter updates in boldface; other parameter estimates same as adult model.^b%CV = $100 \times \frac{SD}{\text{parameter estimate}}$ with SD (standard deviation) from the parameter covariance matrix.^cSource information in references.

Post-thyroidectomy protocol alternatives

Our quantified model approximates average thyroid system physiology of children ranging in age from 3 to 9 years—the age range of the data used to quantify the model. Due to the wide variation in size and other factors in children treated this way, the specific doses used in the following simulations and results do not correspond to a specific age.

Thyroid remnant range for simulation studies. Thyroid remnants are assumed to secrete TH in response to TSH stimulation in proportion to remnant size relative to intact thyroidal tissue (14). We simulated protocols using thyroid remnants ranging from 0.1% to 5% of normal secretion (10–200 mg), to allow for variations in surgery techniques. Based on thyroid size data in children ranging from 3 to 9 years (21), this is equivalent to 0.1% for 9-year-olds with a 10-mg remnant, to 5% for 3-year-olds with ~200-mg remnant. Of note, while the terms of near-total and total thyroidectomy are variably defined in the literature (sometimes including patients with up to 1 g of residual thyroid tissue) (22), highly experienced thyroid surgeons can achieve small thyroid remnant sizes of 10 mg or less, regardless of the patient's age (personal communication from Dr. Michael Yeh, Departments of Medicine/Endocrinology and Surgery, UCLA, January 2011). To incorporate remnant size into the model, we multiplied the normal TH secretion rates SR_3 and SR_4 by the desired percent remnant for the simulations, as in Eisenberg *et al.* (14).

Full replacement and TSH suppression doses. *Simulated full replacement* is the T₃ or T₄ dose rate that approximately normalizes simulated plasma TSH (26 μ g/d LT₃ or 60 μ g/d LT₄ for 1.5–2 mU/L TSH) (19) during replacement in Fig. 1. A *suppressive dose* yields TSH <0.1 mU/L for the majority of the replacement period (50 μ g/d LT₃ or 90 μ g/d LT₄) (5,6).

Withdrawal period. This is the time between stopping replacement and plasma TSH reaching 25 mU/L. In some of our simulations, TSH levels reached 25 mU/L before the end of the replacement period. These are designated as a withdrawal time of 0 days.

Because TSH has a significant circadian rhythm, night-time TSH may exceed 25 mU/L while average TSH remains below the threshold. For practical purposes, we measured withdrawal time in our simulations as the time when the 24-h *moving average* of TSH crosses 25 mU/L, as shown in the graphs.

Withdrawal protocol simulations. We simulated several withdrawal protocols to examine which best minimized withdrawal period while maintaining normal TSH levels during replacement.

1. *T₃ vs. T₄ protocols.* We compared the simulated effects of T₃ versus T₄ replacement on withdrawal time, for a range of remnant (i) and dose (ii) sizes.

- Remnant size. Three weeks of full replacement dosing with either LT₃ or LT₄, for remnant sizes ranging from 0.1% to 5%.
- Dose size. Assuming a remnant size of 2.5% (the approximate midpoint of the range above), we simulated 3 weeks full replacement of T₃ and T₄, using doses ranging from no replacement to full replacement to suppressive doses (0–50 μ g T₃/d, 0–90 μ g T₄/d).

FIG. 3. Fit of T₄ distribution parameters to T₄ tracer data from Haddad (17) scaled to fraction of the dose. No error bars are shown because none were reported in the reference.

2. *Additional T₃ protocols.* Since T₃ has a shorter half-life than T₄, we simulated two additional T₃ protocols to investigate how replacement duration and number of T₃/day doses affect withdrawal period.

- Duration of treatment. Two and 4 days, and 1, 2, and 3 weeks of full replacement T₃, for 2.5% (midrange) remnant.
- Doses/day. Three weeks full replacement T₃, but altered dose frequency (1, 2, 3 times/day), for 2.5% remnant.

Results

Model development

Figure 3 shows that the simulated pediatric TH D&E sub-model plasma T₄ output fitted exceptionally well to the T₄ tracer data, with parameter estimates and variabilities (14%–36% CV range) given in Table 3. Simulated full replacement doses were found to be 26 μ g/d LT₃ or 60 μ g/d LT₄. Quantified model parameters and equations are given in Tables 1–4.

Model validation

Plasma TSH/FT₄ ratio. The simulated average daily TSH/FT₄ ratio was 0.1 mU/pmol, similar to the clinical value of 0.0924 mU/pmol in 4–6 year olds (19).

**TABLE 3. PEDIATRIC THYROID HORMONE D&E MODEL
PARAMETER ESTIMATES AND THEIR VARIABILITIES
BASED ON MODEL FITTING TO HADDAD DATA**

Parameter	Pediatric model estimate (h^{-1}) $\pm$ %CV ^a
k_{02}	$0.0114 \pm 17\%$
k_{12}	$0.523 \pm 19\%$
k_{13}	$0.0514 \pm 29\%$
k_{21}^{free}	$2275 \pm 14\%$
k_{31}^{free}	$255 \pm 36\%$

Data derived from Haddad, 1960 (17) (see Fig. 3).

^a%CV = (SD/mean) $\times$ 100.

TABLE 4. COMPARISON OF PEDIATRIC AND ADULT ESTIMATES

Parameter	Units	Estimate $\pm$ %CV		Source reference ^a	
		Pediatric	Adult	Pediatric	Adults
V_{TSH}	L	2.5	3.5	This study (see Methods)	Eisenberg <i>et al.</i> , 2006 (12)
V_p	L	1	3	This study (see Methods)	Eisenberg <i>et al.</i> , 2006 (12)
k_{02}	h^{-1}	$0.0114 \pm 17\%$	$0.0189 \pm 25.7\%$	This study (see Table 3)	Pacini <i>et al.</i> , 2002 (11)
k_{12}	h^{-1}	$0.523 \pm 9.2\%$	$0.868 \pm 18.3\%$	This study (see Table 3)	Pacini <i>et al.</i> , 2002 (11)
k_{13}	h^{-1}	$0.0514 \pm 28.8\%$	$0.108 \pm 12.4\%$	This study (see Table 3)	Pacini <i>et al.</i> , 2002 (11)
k_{21}^{free}	h^{-1}	$2275 \pm 14.4\%$	1503	This study (see Table 3)	Pacini <i>et al.</i> , 2002 (11)
k_{31}^{free}	h^{-1}	$255 \pm 36.0\%$	584	This study (see Table 3)	Pacini <i>et al.</i> , 2002 (11)
K_{LAG}	unitless	6.5	5	This study (see Methods)	Eisenberg <i>et al.</i> , 2008 (13)
T_{3P}^{EU}	nmol/L	2.6	2	Fisher <i>et al.</i> , 2000 (20)	Eisenberg <i>et al.</i> , 2008 (13)
T_{4P}^{EU}	nmol/L	100.8	93.3	Fisher <i>et al.</i> , 2000 (20)	Eisenberg <i>et al.</i> , 2008 (13)

^aSource information in references.

T₄-based remnant ablation validation. For full T₄ replacement (60 μ g/d), simulated withdrawal times were 7–10 days for 0.1%–5% remnants, similar to clinical results of 1 week (6). For suppressed T₄ replacement (90 μ g/d), the simulated withdrawal times were 12–15 days, similar to reported clinical data, 12.3 ± 0.7 days (6).

Protocol simulations

1. **T₃ vs. T₄ protocols (Figs. 4–7).** Overall, T₃ treatment (Figs. 4 and 6) resulted in shorter withdrawal times than T₄ (Figs. 5 and 7), for both full replacement and suppressed dosing, regardless of remnant size. For smaller doses, the withdrawal times for both T₄ and T₃ were similar to giving no replacement following thyroidectomy, with TSH reaching 25 mU/L before the replacement period ended.

- i. **Remnant size.** Protocol simulation results are shown in Figs. 4 and 5. For T₃ replacement, withdrawal time was

FIG. 4. Predicted impact of thyroid remnant size on triiodothyronine (T₃) withdrawal time. T₃-based remnant ablation protocols with full replacement (26 μ g/d T₃) for differing remnant percentages (0.1%–5%). For all remnant sizes, TSH is within the normal range (shaded gray region) during replacement, reaching 25 mU/L (dashed black line) 3.5 days after withdrawal. Color images available online at www.liebertonline.com/thy

3.5 days for all remnant sizes. For T₄ replacement, the withdrawal time ranged from 7 to 10 days (0.1% remnant, 7.2 days; 0.5% remnant, 7.4 days; 1%, 7.5 days; 2.5%, 8 days; 5%, 9.5 days).

- ii. **Dose size.** Simulation results are given in Figs. 6 and 7. For both T₃ and T₄ replacement, higher doses yielded longer withdrawal times, and lower doses resulted in TSH rising above normal during the replacement period, in some cases exceeding 25 mU/L before the replacement period ended.

For T₃-only replacement, up to 10 μ g T₃/d yielded TSH values >25 mU/L during the replacement period. TSH was above 10 mU/L for 15- and 20- μ g doses during replacement and remained within the normal range for larger T₃ doses, 30 and 50 μ g. During withdrawal of T₃, 15 μ g doses required 2 days withdrawal and 20-, 30-, and 50- μ g doses required 3, 4, and 5 days for withdrawal, respectively.

For T₄ replacement, results were similar, but with somewhat longer withdrawal times were needed to maintain

FIG. 5. Predicted impact of thyroid remnant size on T₄ withdrawal time. T₄-based remnant ablation protocol with full replacement (60 μ g/d T₄) for remnant percentages from 0.1% to 5%. Withdrawal time increased from 7 to 10 days with larger remnant size (see inset graph). In inset, remnant sizes are ordered the same, min to max, top to bottom. Color images available online at www.liebertonline.com/thy

FIG. 6. Predicted impact of T₃ dose on withdrawal time. T₃-based remnant ablation protocols for dose sizes 0–50 µg T₃/d. Twenty-four hour moving average of TSH concentrations. Average TSH levels are maintained in the normal to suppressed range (shaded gray area) during replacement, for both full replacement and suppressing doses. Withdrawal times ranged from 0 to 5 days, with shorter withdrawal for smaller doses. Color images available online at www.liebertonline.com/thy

normal TSH levels. They were 4, 6.5, 8.25, and 11 days for 30-, 45-, 60-, and 90-µg doses, respectively. TSH was within the normal range only for 60 and 90 µg T₄ doses during the replacement period.

2. *Additional T₃ protocols.* Overall, as shown in Fig. 8, neither duration of treatment nor dose frequency had a significant effect on TSH level objectives or withdrawal times.

- i. Replacement duration. For replacement periods ≥ 1 week, withdrawal time was constant at ~ 4 days. Withdrawal time for 2 and 4 days of replacement was 5 days.
- ii. Dose frequency. TSH and T₃ simulation responses to T₃-only dosing are illustrated in Fig. 8. Average T₃ levels during replacement were the same regardless of dose frequency (3.35 ng/mL), but—as shown—daily plasma T₃ oscillations were substantially reduced by dosing more frequently. With one time/day, they ranged from 1.9 to 7.5 ng/mL; for two times/day, 1.8 to 5.26 ng/mL; and for three times/day, 1.7 to 4.6 ng/mL. Simulated TSH was unchanged with dose frequency, and all required a minimum withdrawal time of 3.5 days.

Discussion

Model development and validation

This model was developed on an existing framework (14), updating the brain and thyroid D&E submodels to reflect pediatric physiology and data. The pediatric model was quantified using published pediatric T₄ kinetic data (Fig. 3) as well as steady state T₄, T₃, and TSH serum concentration data, and validated using independent clinical data not used in model development. The model fitted all data well.

In our simulations, we used replacement periods up to 3 weeks prior to testing various withdrawal periods. We recognize that, in clinical settings, the replacement period might be longer than 3 weeks and the dynamics of the rise in plasma

FIG. 7. Predicted impact of T₄ dose on withdrawal time. T₄-based remnant ablation protocol for differing dose size (0–90 µg T₄/d). Twenty-four hour moving average of TSH concentrations during. Average TSH levels are maintained in the normal range (shaded gray area) during replacement period and for full repressed and suppressed doses. Withdrawal times ranged from 0 to 14 days, with shorter withdrawal for smaller doses. Color images available online at www.liebertonline.com/thy

FIG. 8. Top panel: Simulated plasma T₃ during T₃-based remnant ablation protocol for one, two, or three doses per day totaling 26 µg T₃/d, for 2.5% remnant. Average T₃ per day is the same regardless of dose frequency, but T₃ range decreases with more doses per day. Bottom panel: TSH dynamics remained the same regardless of dose frequency.

TSH following hormone withdrawal might vary as a function of replacement period. For lack of data, the model does not account for this possibility, or other clinical variants not tested. We would not, however, anticipate any major changes in our primary results if this were the case. Rather than specify regimens to follow, our results are meant to provide quantitative guidance for developing improved treatment protocols for children, for thyroid surgery as well as in preparation for radioiodine ablation of thyroid remnants following surgery.

Remnant ablation protocols

Different TH withdrawal protocols were simulated in hypothetical 3- to 9-year-old children after thyroidectomy for differentiated thyroid cancer. We compared short-term replacement with T_3 vs. T_4 monotherapy, and predicted the impact of different dosing regimens and thyroid remnant size.

Overall, because TH requirements vary widely across the pediatric age range, dosing designed to either normalize or suppress TSH must be individualized and empirically titrated on the basis of serial thyroid function tests (23). Our simulation results are meant to augment these tests, providing some quantitative kinetics guidelines for finalizing individual protocols. They first of all confirmed that the TSH rise after TH withdrawal is accelerated in children compared with adults (10), consistent with findings in a clinical study of 11 children in which adequate hyperthyrotropinemia was documented within 14 days of LT_4 withdrawal (6). The new model demonstrates a strong positive relationship between either LT_4 or LT_3 replacement and withdrawal, with lower doses yielding shorter withdrawal times (Figs. 6 and 7). Simulated doses ranging from zero to suppressive amounts clearly illustrate that excessive LT_4 dosing prolongs withdrawal times. The "full replacement" LT_4 dose of $60 \mu\text{g}/\text{d}$ was predicted to maintain serum TSH of $1.5\text{--}2.0 \text{ mU}/\text{L}$ during treatment, with a rapid TSH rise to $>25 \text{ mU}/\text{L}$ only 6.5 days after withdrawal. While clinical validation is required, this suggests that certain children could be offered the convenient option of a full replacement postoperative LT_4 dose (rather than a suppressive LT_4 dose), followed by an abbreviated withdrawal of only about a week after complete recovery from surgery. This approach might be appropriate for some cases in which early ^{131}I therapy is desired.

Comparison between T_3 and T_4 full replacement monotherapy (Figs. 4 and 5) predicts much shorter withdrawal times with T_3 (3.5 days) than with T_4 (7–10 days). These several day differences may not be clinically important for some patients, but could be helpful for others. For example, T_3 monotherapy could be used in patients that are kept on T_3 replacement for as long as needed to recover from surgery, then undergo a shorter withdrawal period prior to radioiodine therapy.

Simulated T_3 doses that normalized serum TSH did generate greater than normal plasma T_3 levels, with broad swings over the course of a day (Fig. 8). Dividing administration into two or three separate doses per day substantially decreased the amplitude of these T_3 peaks (Fig. 8) and such T_3 regimens are an established option for withdrawal (24). T_3 values increased to a mean of $3.35 \text{ ng}/\text{mL}$ (normal range $1.2\text{--}2.3 \text{ ng}/\text{mL}$) (19). The same trend is observed in available adult data, where T_3 -only replacement yielded heightened plasma T_3

levels, with some adult patients outside the normal range ($0.8\text{--}1.9 \text{ ng}/\text{mL}$) (25).

Our simulation results also highlight two potentially complicating factors in treatment of thyroid cancer patients following thyroidectomy, namely large thyroid remnants (Fig. 5) or excessive LT_4 replacement (Fig. 7). Both can prolong withdrawal times needed to achieve appropriate TSH levels. The remnant size issue emphasizes the importance of referral to a thyroid surgeon with extensive experience in thyroidectomy as well as a low personal complication rate, to optimize the extent of resection as well as operative risk (26). The excessive replacement issue illustrates the value of postoperative biochemical monitoring to avoid both over- and under-treatment. In contrast to most hypothyroid children who have partial thyroid insufficiency from autoimmune thyroiditis or dyschoronogenesis, postoperative patients are functionally athyreotic and, combined with their rapid T_4 clearance, this leads to early derangement of thyroid status when initial postoperative T_4 or T_3 doses are suboptimal (illustrated in Figs. 6 and 7). Thyroid function tests obtained in all children 2–3 weeks after thyroidectomy could alleviate this complication to assess the adequacy of their replacement.

The simulation results presented here should be useful in formalizing and otherwise guiding new experiment designs specifically addressing thyroid remnant-size effects and enhancements in TH replacement therapy following thyroidectomy in children.

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