A population-based and mixed model approach for enhancing iodine biokinetics in radioiodine therapy for hyperthyroidism

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INTRODUCTION

The development of an individualized dosimetric procedure for radioiodine therapy requires the intensive use of resources in nuclear medicine facilities. In many cases, patient data are too scarce to obtain an accurate estimate of absorbed doses in thyroid. Management of the uncertainty of calculations can be enhanced using statistical tools for population-based approaches. The aim of this work was to build, analyze, and validate a population biokinetic model of thyroid uptake and elimination of radioiodine using a nonlinear mixed-effects approach in patients with Graves' disease through limited sampling of the thyroid uptake curve. A model validated model would allow:
1) An enhanced accuracy in the absorbed dose calculations.
2) The collection of fewer measurements from patients.
3) The completion of patient data if they could not have been properly obtained.

MATERIAL AND METHODS

Input data for the model design were taken from planar scintigraphic images obtained 4, 24 and 96 hours after the administration of a diagnostic activity of radioiodine ^{123}I-NaI. A total of fifty-eight patients who received ^{131}I-NaI for Graves' disease were included in the analysis.

Biokinetic Model Parameters

- U(t): biologic uptake at time t
- A: level of uptake
- K_a: rate of biologic uptake (absorption)
- K_e: rate of biologic clearance (elimination)
- α: between subject variability (random variable)
- N_3: multivariate normal distribution (3-dimensional)
- Σ: variance-covariance matrix
- ε_{ij}: measurement error
- σ^2: variance error
- i: time index (i=1,2,3 with t_1=4 h, t_2=24 h, t_3=96 h)
- j: patient index
- A_m: mean value of level of uptake
- k'_a: natural logarithm of absorption (mean value)
- k'_e: natural logarithm of elimination (mean value)

Statistical Model Design

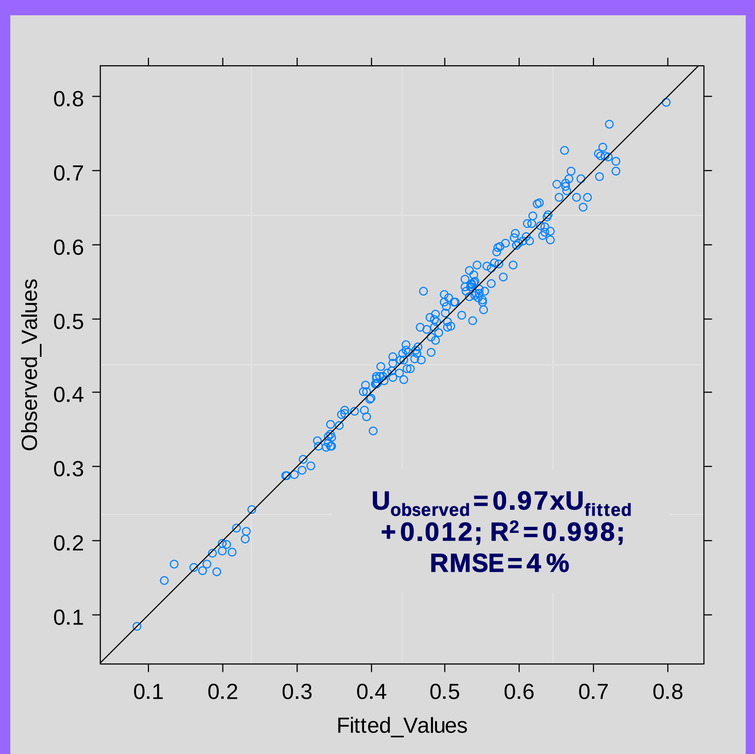
Basic structural model ⟶ $U(t) = -A\,(\exp(-k_a t)-\exp(-k_e t))$
+
Interindividual Variability ⟶ $\alpha \sim N_3(0, \Sigma)$
+
Residual Error ⟶ $\varepsilon_{ij} \sim N(0, \sigma^2)$

⬇

$$U_{ij} = -(A_m + \alpha_{1j})\,[\exp(-\exp(k'_a + \alpha_{2j})t_i) - \exp(-\exp(k'_e + \alpha_{3j})t_i)]$$

Model parameter values were estimated with the maximum-likelihood method. Different metrics as RMSE and R^2, and the leave-one-out cross-validation (LOOCV) method was used to evaluate the validity and predictive ability of the model.

RESULTS



Observed vs. fitted uptake values

In the LOOCV method, an observation is removed, and then the model parameters are fitted again. The removed (unknown) observation is predicted using the parameters of new model. The root mean squared of prediction (RMSEP) was calculated for each removed observation and the therapeutic activity of ^{131}I derived of these predictions was calculated.

Removed Observation [time]	Total number of observations	RMSEP (CV) Predicted Observation Value	RMSEP (CV) Predicted 131I activity (MBq)
One [All]	169	0.059 (12%)	30 (12%)
One [4 h]	58	0.079 (19%)	26 (10%)
One [24 h]	55	0.039 (7%)	22 (9%)
One [96 h]	56	0.053 (11%)	38 (15%)

CONCLUSIONS

Mixed-effects modeling allows the rapid characterization of radioiodine biokinetics with few measurements per patient. This method can be used to enhance calculations for dosimetry accuracy in therapies using ^{131}I as well as to select the optimal working protocol to develop an optimum personalized dosimetric method according to time, organization and facility resources. In our case, with two samples per patient (4 and 96 hours), the calculation of the therapeutic activity of 131I carried a very limited loss of accuracy. This methodology can also be applied in other areas of radiation dosimetry.