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Biokinetic model for treatment planning

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1. Introduction

Bio-kinetic models published by the International Commission on Radiological Protection (ICRP) are based on measurements involving healthy, so-called reference, humans and animals (1, 2). Estimation of radiation doses for a specific patient cohort in nuclear medicine or molecular radiotherapy is often not appropriate using these models (3). Development of a patient-population specific pharmacokinetic model using actual patient data is important to compare the bio-kinetic properties to the established ICRP models and to potentially allow for patient-tailored treatment planning.

Two classical approaches exist in the development of population models (4). In the two-stage approach, the structural models (i.e. compartmental models) are fitted for each subject individually and population rate-constants are estimated as mean rate-constants from the set of individual biokinetic parameters (i.e rate constants). In the naïve pooled approach, the structural model is fitted to the full data-set of the subjects without considering the inter-subject variability. Those classical approaches have been shown to often result in biased parameter estimates. Furthermore, none of the inter-patient variability can be explained, an essential criterion to allow for patient-tailored treatment planning. Those models are, therefore, only able to describe the bio-kinetic behaviour in an "average" subject. And while some attempts have been made in the past to expand the ICRP bio-kinetic models to account for the age and sex of subjects (5), no models have been developed yet that are able to provide more realistic estimates for an individual patient. Bio-kinetic models developed using classical approaches cannot be used to estimate doses for an individual patient.

A population approach using non-linear mixed effects models allows for the inclusion of inter-patient variability. Non-linear mixed effects models consist of fixed and random effects. The fixed effects are implemented in a structural model (i.e. rate constants in the case of a compartmental model). Random effects can be sub-divided into inter-individual variability and residual errors. The inter-individual variability describes how fixed effects in the individual subjects vary from the population fixed effects. The residual errors include any un-observed variability and include for example the measurement errors. Covariates, patient characteristics, can be added to the fixed effects to at least partially explain the inter-individual variability. (4)

A population model was developed based on the data available from MEDIRAD WP3 clinical studies (6) to describe the pharmacokinetics of ^{131}I-NaI in thyroid cancer patients who have had previous thyroidectomy. The population modelling approach had three major aims:

- Extract pharmacokinetic properties of ^{131}I-NaI in thyroid cancer patients after thyroidectomy as rate constants are expected to be very different compared to healthy individuals and patients with hyperthyroidism.
- Identify demographic, pathophysiological or environmental factors that affect the pharmacokinetic properties in the patient population and devise a population model that is able to predict pharmacokinetic properties for individual patients based on a few simple measurements and covariates.
- Identify the possibility to accurately predict thyroid remnant uptake and pharmacokinetic properties in patients not included in this study to aid the treatment planning of 131I-NaI in thyroid cancer patients after thyroidectomy.

The bio-kinetic model was based on the International Commission on Radiological Protection ICRP-128 I-131 (1, 2) and modelling was performed in Monolix (Version 2020R1. Antony, France: Lixoft SAS, 2020).

2. Proof of concept modelling

Feasibility of the modelling was assessed using retrospective data of 23 patients from a previous dosimetry study (7) for whom biokinetic data were available for thyroid remnant, blood, protein-bound-iodine and whole body. The modified ICRP-128 model (see Figure 1) was able to accurately reproduce the activity retention of the retrospective data. The modified model had slower transfer rate constants from blood to thyroid (0.12 day-1) compared to ICRP-128 (7.26 day-1). Thyroid to blood transfer in both models was found to be comparable (30 day-1 and 36 day-1). The model was subsequently further adapted using data acquired as part of the multi-centre multi-national prospective study as part of MEDIRAD WP3.

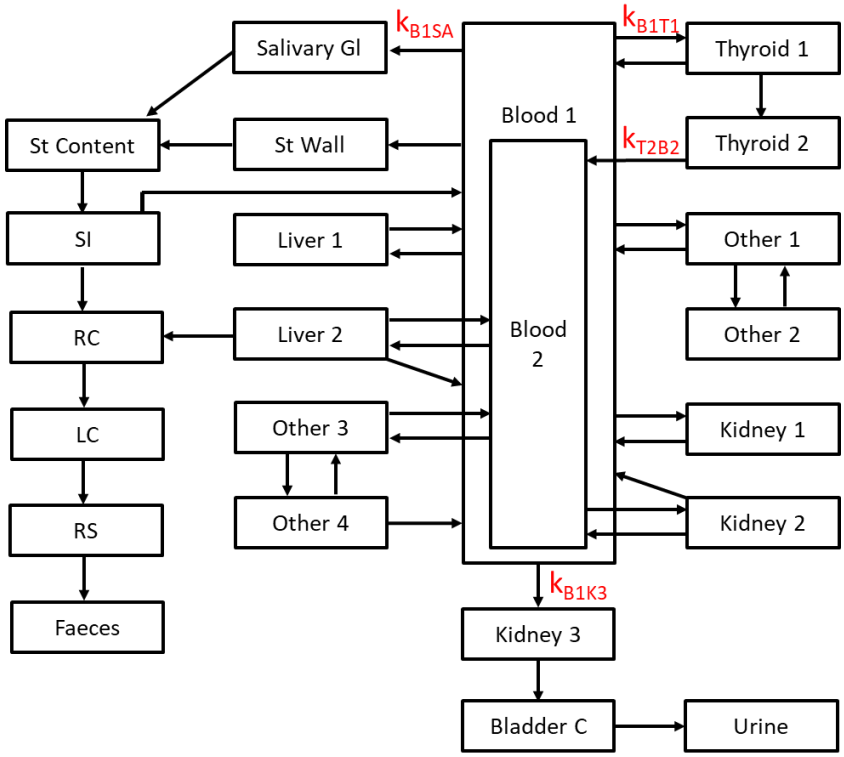

Figure 1: The structural base model implemented in Monolix 2020R2. Rate constants shown in red were tested during the model building process for the MEDIRAD patient data-set. (1, 2)

3. Modelling for MEDIRAD data

3.1 Data & Methods

Inclusion of data in model

Whole-body, thyroid remnant and normal organ activity retention data were available from the clinical studies at four centres as part of WP3. In addition, information was collected on case-report-forms to allow for the inclusion of patient specific covariates for a patient specific model. The patient specific covariates included age, sex, weight, height, pre/post treatment thyroglobulin levels, clinical status and kidney function (estimated glomerular filtration rate - eGFR). All missing covariates for individual patients were replaced by the mean value of the entire patient population included in the study.

Modelling software and bio-kinetic model

Modelling was performed in Monolix (Version 2020R1. Antony, France: Lixoft SAS, 2020). The structural base model as shown in Figure 1 was implemented in Monolix and only rate constants shown in red were allowed to vary based on the available patient data. In Monolix the error model was initially chosen as combined, error distributions were log-normal, parameter distributions were log-normal and random effects were allowed on all adjusted parameters. In the initial model, no correlation between parameters and no covariates were considered. Correlations among the inter-individual variabilities were added to the base model based on the statistical tests available in Monolix. Covariates (patient characteristics) were added to the model to explain the inter-patient variability using systematic procedures and including any scientific evidence (pharmacologic, biologic, pathophysiologic, clinical).

Assessment of model adequacy

Assessment of model adequacy was performed by requiring successful minimisation and visual inspection of diagnostic plots and via the statistical tests in-built in Monolix.

3.2 Results

No significant correlation between random effects of the rate constants for the base model shown in Figure 1 were found (p>0.05 in all cases). The rate constant of blood to kidney 3 (k_{B1K3}) was significantly affected by the kidney function of the patient, measured as the estimated glomerular filtration rate (eGFR). As shown in Figure 2, the rate constant k_{B1K3} increases for patients with better kidney function as indicated by a higher eGFR. eGFR was, therefore, added as covariates on the rate constant k_{B1K3}.

The plots to compare model predictions and measured data for salivary gland, thyroid remnant and whole-body activity retention for the MEDIRAD patients are shown in Figure 3.

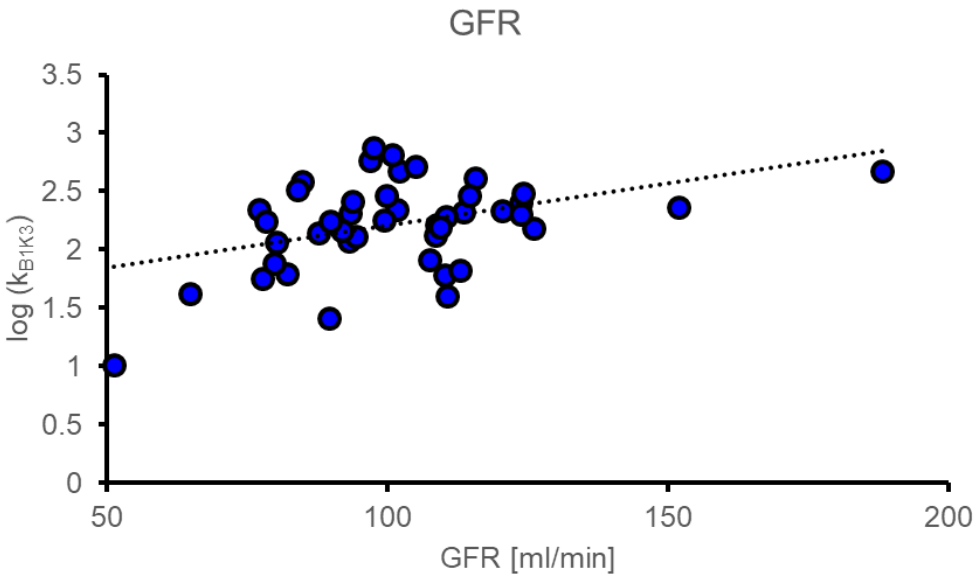

Figure 2: Correlation assessment between the estimated glomerular filtration rate (eGFR) and the rate constant k_{B1K3} from blood to kidney.

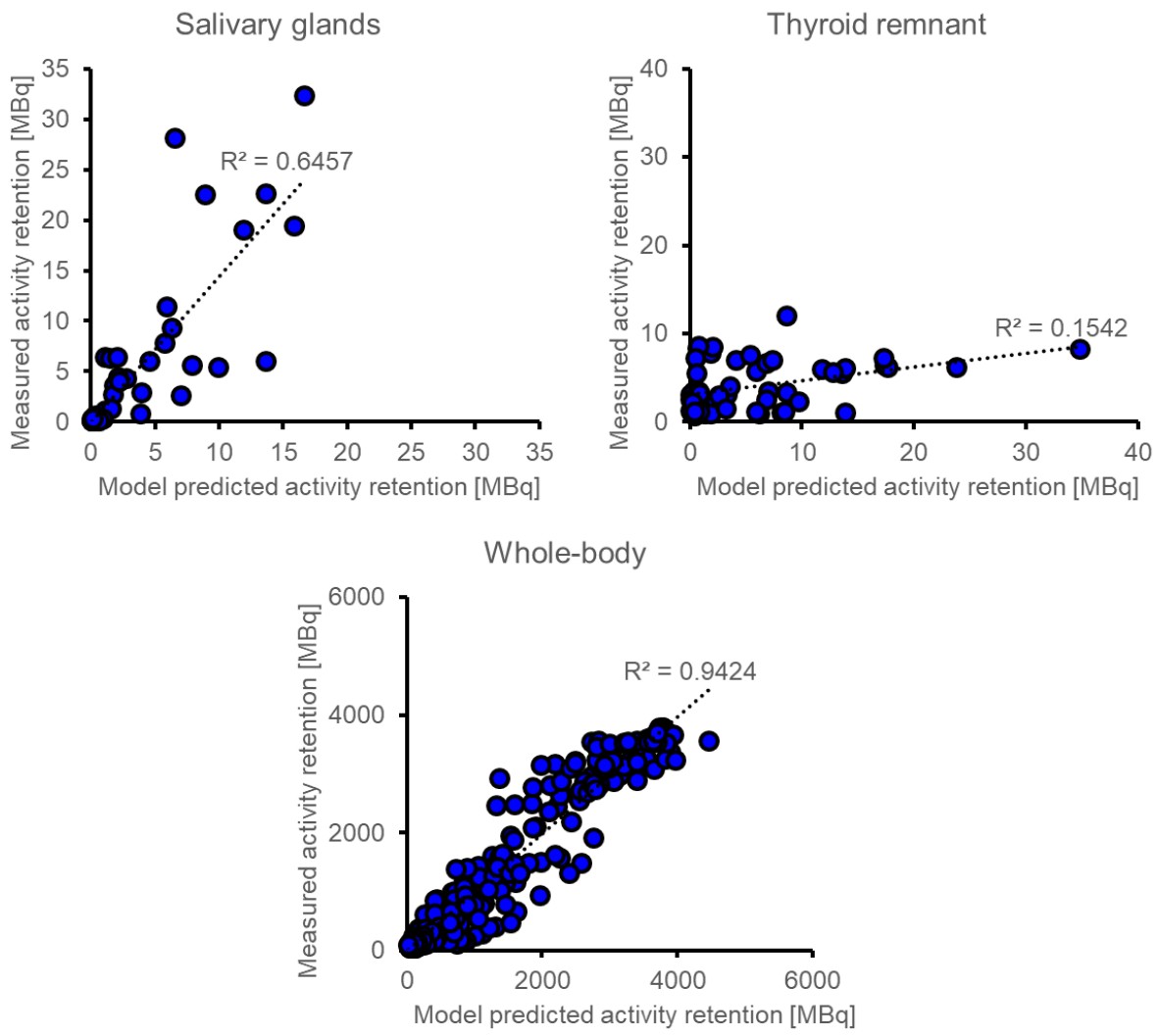

Figure 3: Comparison of the population model predictions including patient specific covariates and measured patient data for salivary gland, thyroid remnant and whole-body activity retention data of the MEDIRAD WP3 clinical studies.

A comparison of the estimated model parameters from the base model to the final model is shown in Table 1. Inter-individual variability remains largely unexplained for the different parameters even after inclusion of patient-specific parameters in the model as indicated by the relatively large deviations of random effects.

Table 1: Comparison of estimated parameters for the base model and the full model presented here.

	Base model parameters	**Base model fit to MEDIRAD data**	**Final model fit to MEDIRAD data**
Fixed effects			
k_{B1T1}^{pop}	0.14	0.09	0.28
β_{kB1T1}^{Centre}	-	-	-2.43
k_{B1K3}^{pop}	6.96	8.86	4.64
β_{kB1K3}^{GFR}	-	-	0.0065

k_{B1SA}^{pop}		5.71	5.91
k_{T2B2}^{pop}	0.35	0.81	0.81
Deviation of the random effects			
ω_{kB1T1}	-	1.88	1.40
ω_{kB1K3}	-	0.35	0.34
ω_{kB1SA}	-	0.69	0.80
ω_{kT2B2}	-	0.00001	0.000033

4. Discussion

A population pharmaco-kinetic model that can describe the bio-kinetic properties of the whole patient population for a diagnostic or therapeutic radionuclide/radiopharmaceutical would be desirable for both radiation protection considerations and treatment planning. Such a pharmaco-kinetic model should be able to accurately predict the bio-kinetic properties of the patient population but also make predictions for individual patients. The latter are essential to potentially allow for patient-tailored treatment planning by combining the predicted bio-kinetic properties to the outcome of treatment for the therapeutic application of radiopharmaceuticals. The developed model in the current study forms the basis of a more complex model for the use of radioiodine after thyroidectomy in thyroid cancer patients.

ICRP models have often only been developed for healthy, reference, humans or animals. It is often unclear how bio-kinetic properties change in a patient population with a certain disease. Furthermore, ICRP models cannot be used to make individual patient predictions. It has been shown here that the development of a patient-population specific bio-kinetic model is feasible even with a limited number of patients and measurements per patient.

The model presented here is able to predict whole-body and salivary gland activity retention of individual patients based on a limited set of covariates with reasonable accuracy. While the standard deviation of the random effects decreased after the addition of covariates, most of the inter-individual random effects remain unexplained in the current model. In the current state, the model is most likely not able to make accurate predictions of individual patient bio-kinetics, especially for activity retention in the thyroid remnant. Differences in the surgical approaches for each patient, but also within centres are a possible reason for the differences in radioiodine uptake following total thyroidectomy. Nevertheless, the model can accurately predict whole-body and salivary gland activity retention and therefore be used to assess radiation doses to dose limiting organs prior to therapy for this patient cohort.

Furthermore, modelling methodologies were also tested on a data set of six patients with metastatic castration resistant prostate cancer (mCRPC) treated with 223Ra-Dichloride. Results suggest that this technique may be expanded to other types of molecular radiotherapy to allow for patient-tailored treatment planning. (8)

5. Conclusion

The ICRP 128 bio-kinetic model was updated and a set of rate constants determined to accurately describe bio-kinetics of a thyroid cancer patient population. The developed model can be used for radiation protection assessments for this patient cohort. Furthermore, the model can potentially be used for personalised treatment planning to assess radiation doses to dose-limiting normal organs.

6. References

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