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Original Paper

A Multi-Compartment Model Capturing the Pharmacokinetics of the Calcimimetic Cinacalcet

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Key Words
Cinacalcet • pharmacokinetics • mathematical model

Abstract
Background/Aims: Chronic kidney disease-mineral bone disorder is a major complication affecting the vast majority of chronic kidney disease patients. A hallmark of the disorder is an altered parathyroid gland biology resulting in secondary hyperparathyroidism. This condition is widely treated by calcimimetics like cinacalcet which act by allosteric activation of the calcium sensing receptor. ***Methods:*** Here, we present a linear multi-compartment model based on physiological principles such as first-pass metabolism and protein binding, which captures all relevant pharmacokinetic parameters of cinacalcet. ***Results:*** Due to the linear structure of the model, simulations are numerically stable and allow fast and accurate short or long-term predictions of cinacalcet concentrations in the body. ***Conclusion:*** The model compartments are physiological meaningful and can be easily adjusted to various conditions like impaired hepatic clearance or different drug administration regimens. Moreover, the model can be easily adapted to specific patient groups.

Introduction

Blood ionized calcium concentrations (Ca^{2+}) have to be maintained within a very narrow range of around 2%; a deviation from this range will result in serious health issues and if persistent in life threatening situations [1]. A key endocrine regulator for Ca^{2+} is the parathyroid hormone (PTH) [2-4]. PTH stimulates bone remodeling thereby ensuring a net release of calcium from the bone storage. Furthermore, it stimulates vitamin D conversion to its metabolic active form 1, 25-dihydroxyvitamin D3, and it inhibits renal phosphate reabsorption while enhancing renal calcium reabsorption. The key regulator for the detection of changes in blood ionized calcium levels and the subsequent secretion of PTH is

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the calcium-sensing receptor (CaSR) on the surface of parathyroid gland (PTG) cells [5-7]. If activated by calcium binding, the CaSR down-regulates PTH production and secretion as well as cell proliferation of PTG cells.

In patients suffering from chronic kidney disease (CKD) the impairment of vitamin D metabolism as well as the impaired clearance of PTH and phosphate by the kidneys trigger a cascade of feedback loops resulting eventually in chronic kidney disease-mineral bone disorder (CKD-MBD). CKD-MBD is a complex disorder affecting the vast majority of chronic kidney disease patients. It is associated with a variety of pathological effects like renal osteodystrophy [8-10] or vascular calcification and an increased risk for cardiovascular events, the leading cause of mortality in CKD patients [11-14]. A hallmark of CKD-MBD is secondary hyperparathyroidism, reduced expression of calcium-sensing receptor and parathyroid gland cell hyperplasia [15-18].

The 2017 KDIGO CKD-MBD Guideline Update suggests maintaining intact PTH levels in the range of approximately 2 to 9 times the upper normal limit for the assay [19]. One strategy to reach this goal is to target the CaSR. Calcimimetic drugs like cinacalcet or etelcalcetide enhance the interaction between the ionized calcium concentration (Ca^{2+}) and the CaSR by allosteric activation [20]. The higher sensitivity of the CaSR to Ca^{2+} leads to an inverse relationship between plasma PTH and cinacalcet concentrations. PTH concentration declines after the administration of cinacalcet until it reaches a minimum approximately 2-3 hours after dosing.

Cinacalcet hydrochlorid, which was approved by the FDA in 2004, is widely used in hemodialysis patients [21] and has been listed under the 100 best selling pharmaceuticals world wide in the last years. In addition to secondary hyperparathyroidism in patients with CKD on dialysis, cinacalcet is also approved for the treatment of hypercalcemia in patients with parathyroid carcinoma, and severe hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy. Its pharmacokinetics are well established in clinical studies [20, 22-26]. Following oral administration the plasma concentration peaks within 2-6 hours. The absolute bio-availability is only between 20-25% while absorption is close to 100% indicating a high first-pass metabolism. Since almost 95% of the drug in the plasma is protein bound, the affect of hemodialysis on the pharmacokinetics of the drug can be neglected [25].

The mechanisms leading to CKD-MBD are many and highly complex. Thus, a multitude of mathematical models were established in order to gain a better understanding of the multidimensional factors controlling the PTH household [27-29] or PTH and bone remodeling [30]. For clinical application any proposed model should be able to predict the state of individual patients and ideally indicate an optimal treatment strategy. Due to the vast clinical use of cinacalcet, a realistic model of CKD-MBD has to feature the use of cinacalcet and its effects. To be of clinical use the cinacalcet model should be readily adaptable to various conditions, such as hepatic impairment enhancing cinacalcet exposure [31]. Moreover, it should be able to reflect different administration scenarios including patient adherence which is known to be poor, due to gastrointestinal side effects and a general high pill load in this patient group [32].

Therefore, the aim of this study was to build a multi-compartment model based on physiological considerations capturing all major pharmacokinetics parameters of cinacalcet. Moreover, the model should allow an intuitive individualization to various conditions or administration regimens and omit any numerical instabilities in order to be easily combined with or incorporated to other physiological models.

Materials and Methods

Pharmacokinetics

The low bio-availability of 20-25% indicates a high first pass metabolism. Hepatic impairment results in higher terminal half-life values (40 - 70% for moderate to severe impairment) and higher total

exposure (2.4 old to 4.2-fold higher in patients with moderate to severe impairment) [31]. Administration with food results in higher bio-availability and consequently higher peak concentrations and total exposure values [32]. Around 95% of the drug is protein bound. Therefore, the effect of hemodialysis on the pharmacokinetics is negligible [26]. The high volume of distribution at steady state of 1000 liters indicates a vast distribution outside the systemic circulation [33]. Experiments with radioactive labeled cinacalcet have shown that the drug peaks at different times in different tissues. Roughly, tissue can be lumped into two groups: one group with short time to peak and one group with longer time to peak operating like a buffer for cinacalcet [33].

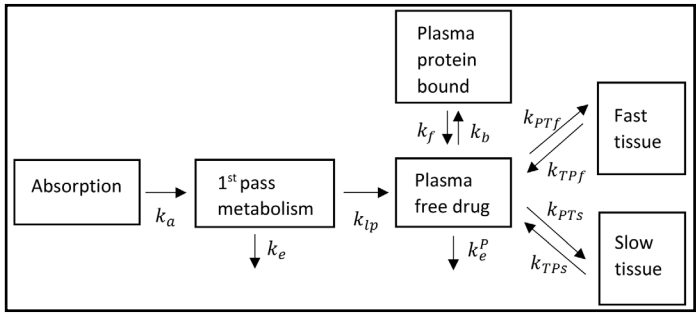

Fig. 1. Pharmacokinetic model of cinacalcet. The absorbed drug has to overcome first pass metabolisms before it enters systemic circulation where it can be bound to protein, eliminated or distributed to the tissue compartments.

Mathematical model

The proposed model is depicted in Fig. 1. We use six physiological motivated compartments, i.e. compartments for absorption, first pass metabolism, plasma free drug and protein bound as well as two tissue compartments. It is notable that the tissue compartment with the longer time to peak can be omitted in most situations reducing the system to 5 compartments. The impact of the sixth compartment on the predictions based the parameter set presented in this manuscript is marginal. However, the tissue compartment with longer time to peak includes adipose tissue and adrenals [33]. Therefore, the six compartment model will be useful when addressing patients deviating from the norm regarding adipose tissue or adrenal gland mass. We use constant rate functions between the compartments. The amount of drug in each compartment can be calculated by solving the following system of linear ordinary differential equations:

$$\frac{d\vec{y}}{dt} = A \cdot \vec{y},$$

where $\vec{y}_1$ corresponds to the amount of drug in the absorption compartment, $\vec{y}_2$ to the amount of drug in the first pass metabolism, $\vec{y}_3$ and $\vec{y}_4$ to the amount of drug in the free and protein bound plasma compartments. $\vec{y}_5$ and $\vec{y}_6$ correspond to the amount of drug in the fast and slow tissue, respectively. The initial dose is delivered to the absorption compartment. In cinacalcet naïve patients the initial condition is given by the vector $\vec{y}_0 = (Administered\ dose, 0, 0, 0, 0, 0)'$. In non-naïve patients the condition for a drug administration at time t_a is $\vec{y}_{t_a} = \vec{y}(t_a) + \vec{y}_0$. The coefficient matrix A can be written as

$$A = \begin{pmatrix} -k_a & 0 & 0 & 0 & 0 & 0 \\ k_a & -k_e - k_{lp} & 0 & 0 & 0 & 0 \\ 0 & k_{lp} & -k_b - k_{PTf} - k_{PTs} - k_e^P & k_f & k_{TPf} & k_{TPs} \\ 0 & 0 & k_b & -k_f & 0 & 0 \\ 0 & 0 & k_{PTf} & 0 & -k_{TPf} & 0 \\ 0 & 0 & k_{PTs} & 0 & 0 & -k_{TPs} \end{pmatrix}.$$

This linear system has the distinct advantage that it can be solved by solving the corresponding eigenvalue problem, i.e. if $\lambda_1,...,\lambda_6$ are the distinct eigenvalues of A and $\Phi=(\vec{v}_1,...,\vec{v}_6)$ is a matrix containing the corresponding eigenvectors, then the solution of the differential equation with the last dose administration at time t_a is

$$\vec{y}(t)=\sum_{i=1}^{6}(\Phi^{-1}\vec{y}_{t_a}')_i\vec{v}_i e^{\lambda_i t},t\geq t_a.$$

Therefore, at any given time t we can calculate the drug amount by evaluating the amount of drug in all compartments only for the preceding administration times. Long time simulations are therefore very fast and numerically stable.

We use data from the literature to estimate the coefficient matrix A. The natural constriction is that all eigenvalues should be distinct and negative to ensure the convergence to zero in all compartments in the absence of further drug administrations. We assume an average plasma volume of 3 liters and a single oral dose of 75 mg cinacalcet if not stated otherwise. The target maximum plasma concentration C_{max} should be close to 26.8 ng/mL, the time until the maximum plasma concentration is reached around 2.3 hours, terminal half-life $t_{1/2}$ 30-40 hours, distribution half-life t_D 6 hours [26, 33]. The apparent oral clearance rate CL/F which is defined as

$$CL/F=\frac{(administered\ dose)}{\int_0^\infty C(\tau)d\tau}$$

should be around 314 L/h [25]. The apparent volume of distribution at steady state V_D which is defined as

$$V_D=(administered\ dose)\cdot\frac{\int_0^\infty t\cdot C(t)dt}{\left(\int_0^\infty C(t)dt\right)^2}$$

should be around 1000 L [25, 33]. Finally, the bio-availability Bio should be between 20 and 25% for fastening patients. We calculate the bio availability as

$$Bio=\frac{\int_0^\infty C_{oral}(t)dt}{\int_0^\infty C_{iv}(t)dt},$$

where C_{iv} is the plasma concentration of the intravenously administered drug. We calculate C_{iv} by analyzing the model modified for intravenous bolus injection. The drug is administered to the "Plasma free drug" compartment thereby omitting the absorption and first pass metabolism compartments. C_{oral} is the plasma concentration of the orally administered drug [25].

Model parameters and sensitivity analysis

Typical model parameters are given in Table 1. We set $k_f=0.0526k_b$ to ensure that 95% of the drug is protein bound in the steady state. For simulations regarding food intake we slightly enhance the absorption rate to $k_a=0.6h^{-1}$ in order to accommodate a slightly lower t_{max} and we reduce the first pass metabolism rate $k_e=0.13h^{-1}$.

Table 1. Model parameters are optimized based on pharmacokinetic data [26, 33]

Parameter	Value
k_a	$0.4\cdot h^{-1}$
k_e	$0.266\cdot h^{-1}$
k_{lp}	$0.09\cdot h^{-1}$
k_e^p	$1\cdot 30\cdot h^{-1}$
k_b	$1\cdot 10^{-5}\cdot h^{-1}$
k_{PTf}	$550\cdot h^{-1}$
k_{TPf}	$0.08\cdot h^{-1}$
k_{PTs}	$50\cdot h^{-1}$
k_{TPs}	$1\cdot 10^{-5}\cdot h^{-1}$

We conducted a sensitivity analysis to study the impact of uncertainties in all parameters in the coefficient matrix A and to identify key parameters of inter-individual variability. The base values of each of these parameters was either divided or multiplied by a factor of 2. We then calculated the respective pharmacokinetic parameters assuming a single dose administration of 60mg cinacalcet. We compared these values to the corresponding base case values. The results are presented in Table 2. The analysis reveals that bio-availability is most sensitive to changes of k_e and k_{lp}. Accordingly, C_{max} is most sensitive to changes of k_e, k_{lp}. Moreover, C_{max} is sensitive to changes of k_{PTf} which determines the buffer function of the tissue. Due to the buffer function of the tissue compartments the terminal half-life is most sensitive to changes of k_{PTf}, k_{PTs} and k_{PTs}. The half-life of distribution as well as t_{max} are sensitive to changes in k_b and k_e. Due to its definition, the apparent oral clearance rate CL/F is only sensitive to changes in k_e and k_{lp}.

Adaptation to specific patient groups

The model can be personalized to individual patients by adjusting the various parameters based on the physiological meaning of the compartments and the sensitivity analysis. As an example we aim to adjust the model to patients with hepatic impairment. It is known that the area under the curve AUC_∞ is 2.4 and 4.2 fold higher in patients with moderated and severe hepatic impairment, respectively, than in healthy control patients. Terminal half-life $t_{1/2}$ is 1.3 and 1.7 fold higher in patients with moderated and severe hepatic impairment, respectively, than in healthy control patients. C_{max} and t_{max} are not significantly altered [31]. The rates associated with liver function are the first pass metabolism rates k_e and k_{lp} as well as the elimination rate k_e^P which is associated with metabolization of the drug by the liver.

Since C_{max} and t_{max} are most sensitive to changes in k_e and k_{pl}, these parameters should not be adjusted. While target AUC and $t_{1/2}$ levels could be reached by adjusting the protein binding rate or the transfer rate to the tissue compartments, the meaningful rate to adjust is k_e^P. We can use the linear structure of the model to calculate the area under the curve AUC_∞:

$$AUC_\infty = \int_0^\infty C(\tau)d\tau = -\left(\sum_{i=1}^{6}\left(\frac{1}{\lambda_i}\Phi^{-1}\vec{y}_0'\right)_i\vec{v}_i\right)_3 - \left(\sum_{i=1}^{6}\left(\frac{1}{\lambda_i}\Phi^{-1}\vec{y}_0'\right)_i\vec{v}_i\right)_4,$$

where the subscripts 3 and 4 denote the third and fourth vector component, respectively. Furthermore, we can use the linear structure of the model to estimate terminal half-life which is associated with the tissue compartments and the largest eigenvalues. Since the fast tissue compartment dominates, we can use the largest eigenvalue λ_k associated with the fast tissue compartment:

$$t_{1/2} \approx \frac{\ln(0.5)}{\lambda_k}.$$

With the parameters set presented in Table 1 the difference between the exact value and the approximated value is less then 0.01%. The reduction of k_l^P by 53% enhances the terminal half-life 1.4 fold and the AUC_∞ 2.2-fold, the reduction of k_l^P by 76% enhances the terminal half-life 1.8 fold and the AUC_∞ 4.2-fold.

Another example would be the administration with food. It has been shown that the administration of a single dose of 90mg cinacalcet with high fat and low fat meal enhances the bio-availability significantly resulting in increase of AUC_∞ of 68% (90% confidence interval: 48% to 89%) and 50% (90% confidence interval: 33% to 70%), respectively [25]. Mean t_{max} is higher in fastening subjects (6h) then in subjects receiving cinacalcet with a high fat diet (4h) and a low fat diet (3.5h). Terminal half-life was comparable between the administration schemes. Since bio-availability is associated with absorption and first-pass

metabolism, the only meaningful parameters to adjust are k_a, k_e and k_{lp}. The sensitivity analysis suggests to decrease k_e and/or increase k_{lp}. Since an increase in k_e would lead to an increase of t_{max} we adjust only k_{lp}.

Results

Main pharmacokinetics profiles

The simulated pharmacokinetics profile of a single oral administration based on the proposed six-compartment model is shown in Fig. 2 and Fig. 3. The results are qualitatively and quantitatively in close agreement with published clinical data.

Table 2. Sensitivity analysis of all estimated model parameters. The base case values where either divided or multiplied by 2. The values, which are rounded to one digit, are the differences to the base cap predictions

Parameter	C_{max} $[ng/ml]$	t_{max} $[h]$	Bio [%]	$t_{1/2}$ $[h]$	$t_{1/2}^D$ $[h]$	VD $[L]$	CL/F $[L/h]$
Base line	25.6	3.1	22.8	35.2	6	1056	339
$k_a \cdot 0.5/\cdot 2$	-7.1/7	1.6/-1.1	0/0	-0.3/0	5.0/-2	62.6/-32.9	0/0
$k_e \cdot 0.5/\cdot 2$	6.9/-7.1	0.9/-0.9	13.6/-9.7	-0.1/0	3.2-/1.9	368/734	-206/696
$k_{lp} \cdot 0.5/\cdot 2$	-11.9/19.5	0.3/-0.4	-9.7/13.6	0/0	0.7/-0.9	807/-403	696/-206
$k_e^p \cdot 0.5/\cdot 2$	1/-1.8	0/0	0/0	4.2/-5.8	0.2 /-0.3	192/-273	0/0
$k_{PTf} \cdot 0.5/\cdot 2$	0/0	0/0	0/0	0/0	0/0	0.5/-0.3	0/0
$k_{TPf} \cdot 0.5/\cdot 2$	-1.5/3.3	-0.3/0.6	0/0	35.2/-17.6	-1.4/3	-175/-13	0/0
$k_{PTs} \cdot 0.5/\cdot 2$	14.4/-10.7	-0.1 /0	0/0	-13.2/26.5	-0.8/0.8	-208/-27	0/0
$k_{TPs} \cdot 0.5/\cdot 2$	0/0	0/0	0/0	0/0	0/0	0/0	0/0

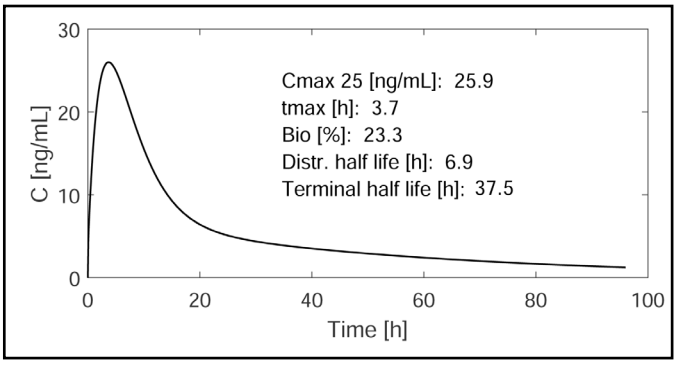

Fig. 2. Cinacalcet concentration versus time after a single 75mg dose. The mean reference values for C_{max} is 26.6 ng/mL (9.4 SD), the reference range for t_{max} is 1-6 hours, for bio-availability (Bio) 20-25 %, and for volume of distribution (VD) 1000-1250 L [25,33]. The reference value for the mean apparent oral clearance rate (CL/F) is 314 L/h (148 SD) [25].

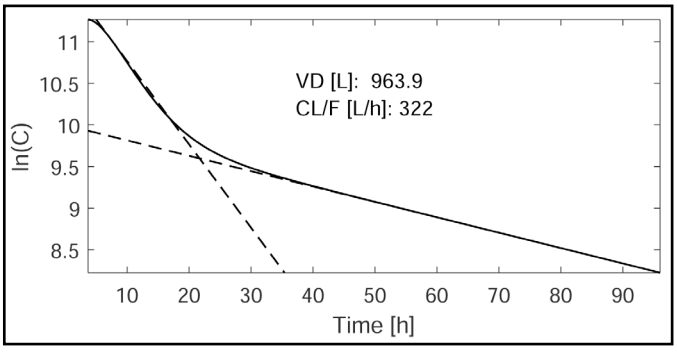

Fig. 3. Cinacalcet concentration versus time after a single 75mg dose (solid line) and the exponential fits used for half-life estimation (dotted lines) on a logarithmic scale. The reference value for the half-life of distribution $t_{1/2}^D$ is 6 hours, the reference range for the terminal half-life is 30-40 hours [25, 33].

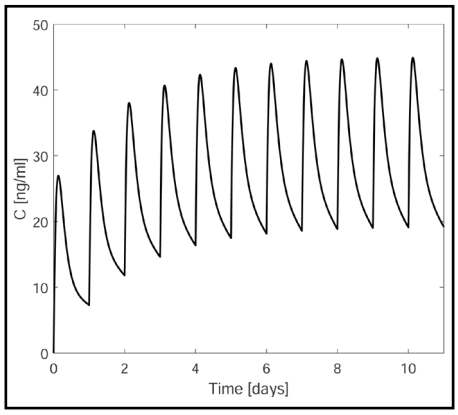

Fig. 4. Cinacalcet concentration versus time based on the assumption that 75mg cinacalcet is administered every 24 hours [25].

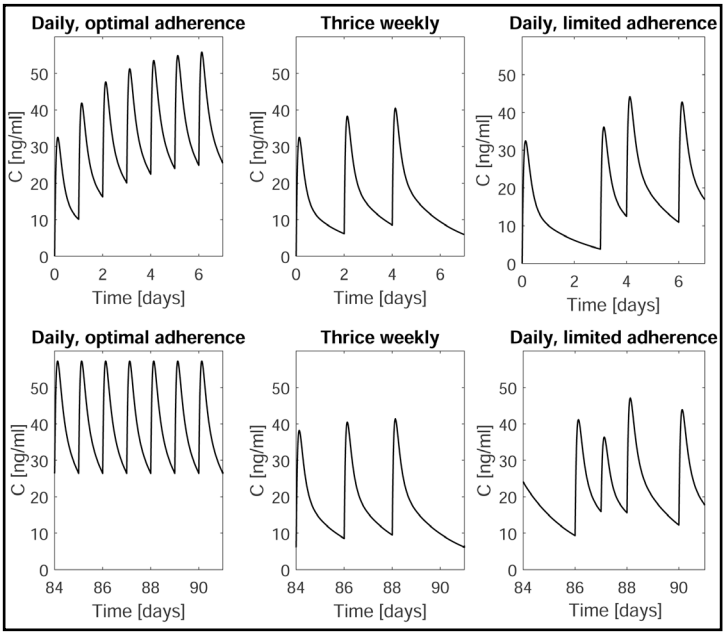

Fig. 5. Drug profiles in cinacalcet naïve patients (upper panel) and in patients after a 12 weeks run in phase (lower panel). While the optimal daily administration leads to higher exposure, reliable three times a week administration is not inferior to a daily administration scheme considering a more realistic adherence rate.

The simulations of daily administration of cinacalcet predict a steady state within seven days (Fig. 4) which is similar to clinically observed behavior of the drug [33].

Different dosing regimens

To assess the impact of dosing regimens on the total exposure we modeled the weekly average cinacalcet concentration in the blood for three different dosing regimens: daily administration, administration three times a week, and administration with a realistic medication refill rate of 64% [34]. For the realistic medication refill rate scenario we chose days without administration randomly (Fig. 5).

Discussion

The linear multi-compartment model introduced in this article is used to describe the complex pharmacokinetic behavior of cinacalcet in the human body. This approach allows the analysis of the effect of different dosing regimens on the drug concentration in

the body that could otherwise only be addressed by clinical studies. The analysis can help to evaluate dose titration and administration schemes. Calcium homeostasis in the human body is achieved by a complex network of regulators, one of them being the kidney. If the kidney function starts to decline, a cascade of physiological processes eventually result in secondary hyperparathyroidism. Due to the complexity of the system, a growing number of mathematical models have been published with the aim to analyze the driving factors of calcium homeostasis, secondary hyperparathyroidism, and CKD-MBD [27, 29, 30, 35-38]. However these models did not include a detailed model of cinacalcet, a drug widely prescribed in patients with secondary hyperparathyroidism. Our pharmacokinetic model can be easily incorporated in all other models by using an operational model of allosterism which transfers the actual Ca^{2+} concentration by the amount of free drug in the plasma [39-41].

It is worth noticing that many model approaches with more than one compartment are able to predict one or two pharmacokinetics parameter within a desired range. The model introduced in this article is minimal in the sense that a linear mass-balance model with less than five compartments is not able to capture all seven key pharmacokinetic parameters (i.e. C_{max}, t_{max}, Bio, CL/F, $t_{1/2}$, $t_{1/2}^{D}$, and VD) simultaneously.

Conclusion

In conclusion, we have developed a mathematical model incorporating key components of cinacalcet pharmacokinetics. A great advantage of this model is its linear structure allowing long term predictions which are fast and numerically stable. The model is a general compartment model which could be used to evaluate different drugs. An example would be etelcalcetide, another calcimimetic which is administered intravenously [42]. In this case the model reduces to a four compartment model since the intestinal absorption and first-pass metabolism compartments are obsolete. Due to the physiological meaningful compartments, adjustments to conditions like hepatic impairment are straight forward. Combined with a model for the parathyroid gland and bone metabolism it provides a ready to use tool for clinical trial simulations to explore effects of relevant factors, such as patient adherence, off-label administration regimens, or the effect of administration combined with food intake.

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Disclosure Statement

Peter Kotanko holds stock in Fresenius Medical Care. The other authors have no conflicts of interest to declare.

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