Intestinal absorption of strontium chloride in healthy volunteers: pharmacokinetics and reproducibility

A. J. A. M. SIPS,¹ W. J. F. van der VIJGH,² R. BARTO² & J. C. NETELENBOS¹

¹Department of Endocrinology, and ²Clinical Research Laboratory of Internal Medicine, Free University Hospital, Amsterdam, The Netherlands

- 1 The absorption kinetics of orally administered strontium chloride and its reproducibility were investigated in healthy volunteers after administering strontium either under fasting conditions (study I, $n=8$) or in combination with a standardized meal (study II, $n=8$). Each subject received strontium orally at day 0, 14, and 28 and intravenously at day 42. The study was performed as part of a project in which a simple clinical test for measuring intestinal calcium absorption is being developed, based on the use of stable strontium as a marker.
- 2 Plasma strontium concentration–time curves were analysed by noncompartment analysis and a four compartment disposition model. Within a volunteer each oral curve was fitted simultaneously with the intravenous curve, by which means a two segment model for absorption was revealed.
- 3 Mean absolute bioavailability of strontium was 25% without a meal and 19% with a meal, whereas the intraindividual variation was 24% and 20%, respectively.
- 4 Various limited sampling absorption parameters were determined in order to select a potential test parameter for measuring intestinal calcium absorption using strontium as a marker. Fractional absorption at 4 h ($F_{c_{240}}$), obtained after co-ingestion of strontium with a meal, appeared to be the best test parameter, because it represented bioavailability well ($r=0.90$).

Keywords pharmacokinetics intra-individual variation strontium intestinal absorption

Introduction

The pharmacokinetics of radioactive strontium have already been the subject of a number of studies [1–3], both because strontium has been used as a marker for calcium metabolism (^{85}Sr , ^{89}Sr) [4–6] and because it is an important product of nuclear fallout (^{90}Sr). In recent years sensitive methods for determining stable strontium have become available [7, 8] and strontium is suitable as a clinical and diagnostic tool for measuring calcium metabolism in humans.

Despite previous studies, there still is a paucity of information on the absorption kinetics as well as on the long-term pharmacokinetics of strontium, and the reproducibility of its pharmacokinetic parameters. There

is a special need for reliable data on the reproducibility of the absorption kinetics since stable strontium is applied as a diagnostic tool for obtaining information about intestinal calcium absorption and about its modulation by intervention therapies [9–11]. Moreover, a simple parameter which correlates well with intestinal absorption (=absolute bioavailability) can be derived from these data. Therefore, the purpose of our study was to assess the pharmacokinetic parameters of strontium and their intraindividual and interindividual variations after orally and intravenously administered strontium chloride in a group of healthy male volunteers, in which strontium was either administered under fasting conditions or in combination with a standardized meal.

Correspondence: Dr W. J. F. van der Vijgh, Free University Hospital, Clinical Research Laboratory of Internal Medicine/BR232, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

Methods

Subjects

Per study (study I=without a meal, study II=with a meal) eight healthy male adults agreed to participate. Both studies were approved by the ethics committee of the Free University Hospital, Amsterdam. All procedures followed were in accordance with the Declaration of Helsinki. The subjects were in good physical condition and no subject took any medication during and at least 1 week before the study. The mean age of the volunteers was 26.2 years (range 21–31 years) in study I and 27.0 years (range 19–30 years) in study II. The mean body weight in the two groups was 73.5 ± 7.1 kg and 78.6 ± 7.0 kg, respectively, with corresponding Quetelet indices of 22.2 (range 19.6–24.7) and 22.8 (range 21.2–24.7).

Study

In both studies, each subject received an oral dose of strontium chloride at day 0, 14 and 28 (=test 1, 2, and 3) and an intravenous injection at day 42 (=test 4). With this design it was possible to assess the absorption pharmacokinetics, including the absolute bioavailability of strontium three times per individual.

Test procedure

All subjects came in the hospital after overnight fasting. The test conditions are summarized in Table 1. The oral dose was administered in 200 ml distilled water and was taken within 1 min, whereas the intravenous dose was dissolved in 4 ml 0.9% NaCl and injected within 2 min. Both formulations were prepared by the Pharmacy Department of the Free University Hospital, using $\text{SrCl}_2 \cdot 6\text{H}_2\text{O}$ (Merck, Amsterdam, The Netherlands) and for study I also $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ (Baker, Deventer, The Netherlands).

In study II the test solution was given in the middle of a standardized meal, which consisted of 150 g Fortipudding with vanilla flavour (Nutricia, Zoetermeer, The Netherlands). Both the pudding and the test

solution were consumed within approximately 3 to 4 min. The pudding is a semi solid ready to eat nutritional supplement. In study II, the Fortipudding was given 1 h before the intravenous dose for obtaining a Ca/Sr ratio in the blood, which is comparable to the ratio after oral administration. In both studies, subjects were allowed to drink and eat *ad libitum* from 2 h after the intake of the test solution. At the start of each test, blood was sampled for serum calcium, albumin, alkaline phosphatase, γ -GT, creatinine, parathyroid hormone (PTH), 25(OH)vitamin D and 1,25(OH) $_2$ vitamin D. After the oral intake of the strontium containing solution, blood samples (2 ml) were withdrawn via an indwelling catheter at 0, 7, 15, 30, 60, 90 min, 2, 3, 4, 5, 8, 24, 32 h, and at 2, 5, 7, 9, 12, and 14 days. In test 4, when strontium was injected intravenously, additional blood samples were withdrawn at 2, 5, 20, and 45 min. Blood was collected into heparinized tubes and centrifuged at 1500 g for 10 min. Subsequently, plasma was separated and stored at -20°C until analysis. All plasma samples were analysed for strontium by graphite furnace atomic absorption spectrophotometry [7]. The limit of detection was 0.21 nmol l^{-1} . The intra-assay precision was 2.2% at approximately 5 nmol l^{-1} and 1.1% at 50 nmol l^{-1} . The inter-assay precision was 0.7% and 1.5%, respectively.

Data analysis

For each subject, four plasma strontium concentration–time (C – t) curves were obtained. All concentrations measured were corrected for endogenous strontium concentrations, determined at $t=0$ of test 1. Nevertheless, the concentrations at $t=0$ of test 2–4 were higher than zero, indicating that strontium was still present in the plasma from the preceeding test(s). Therefore, the C – t curves of test 2, 3, and 4 were corrected for the rest concentrations in the following way. For test 2 and 3, expected values of C_{14d} (= strontium concentration at 14 days following administration of strontium) were related to C_{max} by:

$$C_{14d,n} = \frac{C_{\text{max},n}}{C_{\text{max},1}} * C_{14d,1}$$

in which n represents test 2 or test 3. Since the measured values of $C_{14d,2}$ were higher than the expected values of $C_{14d,2}$, the difference between these values (=rest values) must belong to the terminal phase of test 1. From $C_{14d,1}$ and this rest value at $C_{14d,2}$ the terminal half-life for test 1 could be calculated for each subject. The half-life times obtained, implied that not only $C_{14d,2}$, but also $C_{14d,3}$ contained a rest value of test 1. By subtracting the rest values of test 1 and test 2 at day 28 from $C_{14d,3}$, the terminal half-life of test 2 could also be obtained. The mean of the half-lives obtained for test 1 and test 2 was considered to be the terminal half-life of strontium in a certain subject.

Subsequently, the calculated terminal half-lives were used to correct the plasma C – t curves of test 2, 3 and 4

Table 1 Test conditions in the pharmacokinetic studies

	Study I	Study II
Oral		
Dose	2.5 mmol SrCl_2 + 2.5 mmol CaCl_2	5.0 mmol SrCl_2
Test condition	No meal	150 g Fortipudding (including 9.0 mmol Ca)
Intravenous		
Dose	1.2 mmol SrCl_2	1.2 mmol SrCl_2
Test condition	No meal	150 g Fortipudding (including 9.0 mmol Ca)

for the declining value of $C_{0,n}$ ($=C_{14d,n-1}$) over the subsequent time intervals.

These terminal half-lives were also used to extend each corrected $C-t$ curve by calculating plasma concentrations at 7, 14 and 21 days after $C_{14d,n}$ to include the terminal phase in the pharmacokinetic curve fitting procedure.

Pharmacokinetic analysis

The plasma $C-t$ curves were analysed by compartment independent and compartment dependent pharmacokinetic models using the pharmacokinetic and pharmacodynamic data analysis system Topfit 2.0 [12]. The compartmental modelling by this computer program runs by a three stage optimization algorithm for non-linear least-squares regression that combines a one-dimensional direct search with modified versions of the Hooke-Jeeves vectorial search and Marquardt/Gauss-Newton procedures [12, 13]. For both the compartment-independent and the compartment-dependent models, the following variables were calculated by the program: AUC ($\mu\text{mol l}^{-1} \text{ h}$), MRT (h), CL (ml min^{-1}), $V_{d,ss}$ (l), the terminal half-life $t_{1/2,d}$ (h). The volumes of distribution (V_x) and the disposition and elimination half-life times ($t_{1/2,z}$) were additionally calculated by the compartment model. The absolute bioavailability was calculated from the ratio of AUC after an oral dose and AUC after an intravenous dose, in which both areas were normalized for the dose. Approximately 5–10% of the AUC values were obtained by extrapolation. Absolute bioavailability obtained with this method represents true absorption.

Per subject, the plasma $C-t$ curves obtained after the intravenous dose were fitted by compartment modelling with a weight factor of $1/y^2$. The goodness-of-fit was evaluated by the method of least squares, the Akaike test, the Schwarz test and the Imbimbo test. Subsequently, the disposition and elimination parameters for the selected compartment model were fixed and used for fitting the $C-t$ curves after oral administration (simultaneous modelling). These curves were fitted with a weight factor of $1/y$ in order to obtain a good fit for the absorption phase. Based on the selected compartment model the following parameters were calculated in addition to the above mentioned parameters: lag-times (t_{lag}), absorption rate constants (k_{xx}), mean residence time of absorption (MRT_{abs}) and the fraction of the amount absorbed at locus i (a_i). In all subjects the absorption parameters were calculated for the three oral curves. Finally, for each curve an absorption profile was calculated, by which means the time at which 50% and 90% of the absorption was completed was derived.

Limited sampling absorption parameters

Various limited sampling absorption parameters were determined for test 1, 2 and 3 in order to select a potential test parameter representative for intestinal

absorption. First, parameters described in the literature were calculated, i.e. the fractional absorption at 60 (Fc₆₀) [14] and 240 min (Fc₂₄₀) [15, 16]:

$$Fc_t = \frac{[C_t - C_0] * V}{D}$$

in which C_t = plasma concentration at t min, C_0 = plasma concentration at 0 min, V = volume of distribution represented by 15% of the body weight, and D = dose. AUC(0, 60 min) and AUC(0, 240 min) (=area under plasma concentration–time curve over the interval 0–60 and 0–240 min, respectively) were assessed, because of an expected improvement of precision by using a parameter based on more than one concentration. Moreover, Fc₉₀, Fc₁₂₀, Fc₁₈₀, and Fc₃₀₀ were calculated as potential test parameters.

Statistics

Intraindividual variation and interindividual variation were assessed for all absorption parameters by means of one-way analysis of variance (ANOVA) and expressed as coefficient of variation. The difference in intraindividual variation in study I and study II was tested for significance by a Wilcoxon rank test (unpaired). Correlations between limited sampling absorption parameters and absolute bioavailability were calculated by correlation analysis after statistics revealed a normal distribution for all parameters.

Results

For all subjects the biochemical parameters of calcium and bone metabolism were within the normal range in both studies. Endogenous plasma concentrations (mean $\pm$ s.d.) of strontium were $0.15 \pm 0.05 \mu\text{mol l}^{-1}$ in study I and $0.20 \pm 0.03 \mu\text{mol l}^{-1}$ in study II. After oral administration of the test solution the mean maximum plasma concentration was $25.07 \pm 6.70 \mu\text{mol l}^{-1}$ ($n=24$) and $32.97 \pm 8.28 \mu\text{mol l}^{-1}$ ($n=24$) in study I and study II, respectively. In both studies this maximum concentration was reached at a mean time of 2.9 h (s.d. 0.73 h in study I, s.d. 0.63 h in study II). After the maximum concentration was reached, plasma concentrations of strontium declined due to (re)distribution and elimination from the plasma.

Pharmacokinetic modelling revealed a four compartment model as the best model to fit our data ($r^2 \geq 0.994$). In both studies, an inflexion point was present in the rising part of the plasma $C-t$ curves obtained after oral administration (Figure 1). Therefore, the standard four compartment model was adapted to two segment absorption (Figure 2). This two segment absorption model represents two separate first order absorption processes starting at different lag-times. However, the model does not rule out distinct absorption over the entire gut length, as represented by the absorption constant k_{01} . By this means a substantial improvement of the fit of the absorption phase of the

Figure 1 Three plasma *C-t* curves over 8 h after an oral intake of 5.0 mmol SrCl₂ with a meal within one representative subject.

Figure 2 The four compartment model adapted to two segment absorption as applied in study I and II.

plasma *C-t* curves was obtained ($r^2 \geq 0.998$ for the whole curve). In the model, strontium is directly injected in the central compartment (=compartment 1) for intravenous administration, whereas the compartments 5, 6 and 0 are added to the model for the two segment input after oral administration. The peripheral compartments are represented by the numbers 2–4. Elimination occurs from the central compartment as indicated by

the black arrow. The pharmacokinetic parameters for study I and study II, derived by compartment modelling as well as noncompartment modelling of the plasma *C-t* curves after intravenous administration of strontium, are shown in Table 2.

Within each study, almost identical values were obtained for the pharmacokinetic parameters after compartment and noncompartment modelling. The values of the pharmacokinetic parameters were also almost identical between the studies.

The results obtained with the four compartment model for the *C-t* curves after oral administration of strontium chloride are given in Table 3. Due to the inflection point in the rising part of the *C-t* curve, two lag times with a difference of about 1 h are found. The absorption rate constants k_{50} , k_{60} and, k_{01} were respectively 1.88 ± 0.84 , 2.03 ± 1.89 and, $4.24 \pm 2.10 \text{ h}^{-1}$ in study I and 4.86 ± 6.04 , 2.32 ± 2.05 and, $2.85 \pm 2.04 \text{ h}^{-1}$ in study II. From the absorption parameters calculated by means of the pharmacokinetic modelling a further description of the absorption kinetics was made for each plasma *C-t* curve by means of an absorption profile. Such a profile shows the cumulative absorption (%) as a function of time, in which 100% corresponds with the total amount absorbed (Figure 3). In study I, absorption was almost completed (95%) after $3.0 \pm 0.9 \text{ h}$ ($n=3$ tests in seven subjects) and in study II after $4.3 \pm 2.0 \text{ h}$ ($n=3$ tests in five subjects). In one subject in study I a significantly longer absorption time ($39.2 \pm 0.3 \text{ h}$) was observed, which was consistent throughout the three tests. In order to ensure that the inflexion point observed in the plasma *C-t* curve and the two corresponding time lags were due to absorption from two different loci and not for example due to fractionated release by the stomach, the curves were fitted again with k_{01} fixated at 999 h^{-1} . In this way it was simulated that absorption took place at two loci represented by k_{50} and k_{60} . Subsequently, the distribution of the values for k_{50} and k_{60} were tested for clustered distribution. This test however, did not demonstrate a biphasic distribution.

The intraindividual variation of the parameters describing the absorption kinetics (Table 3) was substan-

Table 2 Pharmacokinetic parameters (mean s.d.) of stable strontium obtained by noncompartment modelling and by using a four compartment model after the intravenous administration of SrCl₂ either without a meal (– meal) or with a standardized meal (+ meal). Each group consisted of eight healthy male adults

	Study I (– meal)		Study II (+ meal)	
	NCA	CA	NCA	CA
$t_{1/2,e}$ (days)	7.5 (2.3)	7.5 (2.3)	7.9 (3.1)	7.9 (3.1)
AUC ($\mu\text{mol l}^{-1} \text{ h}$)	2049 (558)	1950 (551)	1900 (340)	1776 (296)
MRT (days)	5.2 (1.0)	5.5 (1.0)	5.3 (0.8)	5.5 (0.8)
CL (ml min^{-1})	9.6 (2.7)	10.1 (3.2)	10.8 (2.0)	11.5 (2.0)
V_{ss} (l)	70.7 (18.6)	79.0 (22.4)	80.2 (6.2)	89.4 (8.9)
V_c (l)	–	9.8 (3.0)	–	12.3 (4.2)
$t_{1/2,a}$ (h)	–	0.12 (0.07)	–	0.13 (0.10)
$t_{1/2,b}$ (h)	–	3.0 (1.6)	–	2.5 (1.3)
$t_{1/2,c}$ (h)	–	32.3 (13.4)	–	30.4 (10.0)

*NCA, noncompartment modelling. CA, compartment modelling using a four compartment model.

Table 3 Effects of a meal on the within-subject and the between-subject variation of the absorption parameters of orally administered SrCl_2

	Study I (– meal)			Study II (+ meal)		
	Mean	Within subject (CV)*	Between subject (CV)*	Mean	Within subject (CV)*	Between subject (CV)*
$t_{\text{lag},1}$ (h)	0.08	51	46	0.06	92	33
$t_{\text{lag},2}$ (h)	1.44	30	23	0.78	47	19
50%-abs (h)	1.22	24	30	1.57	23	15
90%-abs (h)	2.54	27	30	3.42	37	34
MRT^{abs}	1.33	20	9	2.11	49	22
a_1	0.67	14	12	0.29	85	26
AUC ($\mu\text{mol l}^{-1} \text{h}$)	1107	24	15	1393	20	18
F (%)	25	24	15	19	20	19

*Variation calculated by means of one-way ANOVA and expressed as coefficient of variation.

Figure 3 Representative absorption profiles, in a healthy subject after oral administration of 2.5 mmol SrCl_2 under fasting conditions (a), and 5.0 mmol SrCl_2 following a standardized meal (b).

tial. Only for the AUC and the absolute bioavailability (F) a significant reduction ($P < 0.05$) in the variation was obtained by administering strontium in combination with a standardized meal.

This reduction was also demonstrated for the limited sampling absorption parameters, except for Fc_{60} , Fc_{90} and $\text{AUC}(0, 60 \text{ min})$ (Table 4). The absorption variables based on more than one sample $\text{AUC}(0, 60 \text{ min})$ and $\text{AUC}(0, 240 \text{ min})$ only had a slightly lower intraindividual variation than the corresponding limited sampling parameters Fc_{60} and Fc_{240} . Of these limited sampling

parameters, Fc_{300} correlated best with the absolute bioavailability in study I and Fc_{240} in study II (Table 4).

Discussion

The results of the pharmacokinetic studies reported here, do not only give information about the absorption kinetics of stable strontium and its reproducibility, but also have implications for clinical tests measuring intestinal calcium absorption.

Pharmacokinetic modelling of the plasma C - t curves after intravenous administration demonstrated the best fit for a four compartment model. Both for calcium and strontium such a model was described earlier [17–21], although also two compartment [3] and three compartment [2] models have been reported. The values for the pharmacokinetic parameters derived with the four compartment model were almost identical to the values of the parameters derived with noncompartment analysis. This underscores, in addition to the statistics, that the four compartment model describes the plasma C - t curves well. Moreover, it confirms the use of simultaneous modelling; in compartmental modelling the intraindividual estimates are conditioned on fixing the disposition parameters but the noncompartmental analysis does not suffer from this shortcoming.

In the compartment model, the central compartment (=compartment 1, Figure 2) is thought to represent plasma and extracellular fluid, whereas the apparent volume of distribution at steady state ($V_{d,ss}$) represents the total exchangeable pool for strontium. The values obtained in this study, approximately 10 and 80 l respectively, are comparable with values reported earlier [2, 19]. The clearance of strontium from the central compartment was approximately 10.5 ml min^{-1} , a value which is similar to that reported by others [2, 22]. The terminal elimination half-life of strontium (Table 2) was, however, three to four times longer than the half-life generally found (2.0 days) [3, 10, 18]. This might be due to the fact that we could calculate the half-life over

Table 4 Mean values, correlation with bioavailability, within-subject variation and between-subject variation of the limited sampling parameters in study I and II

Parameter	Study I (– meal)				Study II (+ meal)			
	Mean	r*	Within subject (CV)	Between subject (CV)	Mean	Within subject r*	Between subject (CV)	(CV)
Fc ₆₀	0.069	0.45	20	12	0.027	0.23	33	51
Fc ₉₀	0.083	0.35	23	11	0.051	0.62	23	28
Fc ₁₂₀	0.095	0.49	28	16	0.065	0.79	19	17
Fc ₁₈₀	0.107	0.60	29	16	0.074	0.84	20	15
Fc ₂₄₀	0.096	0.66	29	14	0.070	0.90	20	19
Fc ₃₀₀	0.080	0.84	34	15	0.062	0.83	22	21
AUC (0, 60 min)†	8.4	0.39	21	10	4.1	0.23	66	44
AUC (0, 240 min)†	73.2	0.61	24	7	84.5	0.79	17	14

*Correlation with the bioavailability. †In $\mu\text{mol l}^{-1} \text{ h}$. CV, Coefficient of variation (%).

a period of up to 6 weeks (based on the values of C_{14d} in three subsequent tests). Our finding is underscored by studies of Moraes *et al.* [2, 24], in which a terminal elimination half-life of 5.5 to 6.0 days was found. Moreover, we calculated for our data also a half-life of approximately 2.0 days, when only the period of one test (14.0 days) was taken into account. Like Moraes *et al.* [2, 24], we found in our population a large interindividual variability for the terminal half-life (4.0–12.9 days). Although we did not calculate the intraindividual variation of this parameter we can conclude that this variation has to be small, since the terminal phase of the intravenous curve fitted well to the terminal phases of the oral curves. In a study by Likhtarev *et al.* [1], the intraindividual variation on strontium retention was estimated to be less than 6%. These observations justify our study design, in which we assumed the distribution and elimination parameters to be constant over the period of testing.

The mean absolute bioavailability of strontium chloride was 24% in study I and 19% in study II. This difference in absolute bioavailability in both studies might be caused either by the influence of the meal or by the different calcium/strontium ratios (1.0 in study I and 1.8 in study II) of the test solution administered. Because of the differences in test conditions, we cannot compare the absolute values of the absorption parameters. However, the intraindividual variation and interindividual variation of both studies can be compared.

In both studies the absorption phase of strontium was characterized by an inflexion point. Such an inflexion point was described earlier by Leeuwenkamp *et al.* [3], who interpreted this as absorption from two different intestinal loci playing a dominant role in absorption. In 1969, Birge *et al.* [17] already described a comparable model for intestinal calcium absorption, in which the first locus corresponded with the duodenum and the first portion of the jejunum, and the second locus was represented by a segment of the gut distal from the first locus. Since the transit time of a liquid meal through the small intestine was estimated at 1.2 h to 1.9 h [25], the lag times obtained for the second

locus suggests a location of this locus at the end of the small intestine. A more exact localization cannot be determined from the studies reported here. The absence of a biphasic distribution of k_{50} and k_{60} may on the other hand suggest that strontium is not absorbed from two distinct loci, but is intermittently released by the stomach. However, it seems more plausible that also for strontium two loci may play a dominant role in absorption, but that the absorption rate constants for these loci are approximately equal. This would be in agreement with the absorption rate constants obtained by Leeuwenkamp *et al.* [8], which were also almost equal. Also the time at which 90% of the absorption was completed was comparable with that obtained for calcium [26]. Summarizing these observations, it is plausible that strontium is absorbed from the same sites in the intestine as calcium.

The intraindividual variation for the absolute bioavailability was 24% in study I and 20% in study II. These values seem to be very high in comparison with the values reported for calcium. However, the presentation and the calculation of this variation of absorption parameters for calcium are often misleading. For instance, deGrazia *et al.* [27] performed in seven patients two studies on the absolute bioavailability of calcium by using the balance method in combination with an intravenous dose of ^{47}Ca , in which a mean absorption difference of 8.4% was calculated in the first and second test. However, this difference varied from 0 to 19%, in which in three out of seven subjects the difference was 16% or more. Recalculating the data of deGrazia *et al.* [26] by means of ANOVA also revealed a intraindividual variation of 24%.

For the limited sampling absorption parameters the intraindividual variation was improved by co-ingesting the strontium containing solution with the meal. This improvement was already demonstrated by Milsom *et al.* [16] for Fc₂₄₀. In study I Fc₃₀₀ demonstrated the highest correlation with absolute bioavailability and Fc₂₄₀ in study II. The intraindividual variation of both the absolute bioavailability and these absorption variables was improved by administering strontium in combination with a meal instead of during fasting

conditions. The choice for F_{c240} as a test parameter is underscored by the absorption profile which demonstrates that at that time 90 to 95% of the absorption is completed. Parameters at earlier time points do not take the second absorption locus into account and parameters at later time points are dominated by distribution and elimination.

It can be concluded that the absorption kinetics of strontium chloride follow a two segment absorption, regardless of the presence of a light meal. The absolute bioavailability (=true absorption) was 25% in study I (without a meal) and 19% in study II (with a meal). The absolute bioavailability and the fractional absorption at 4 h demonstrated a intraindividual variation of 24% and 29%, respectively. These variations were both significantly reduced to 20% when strontium was administered in combination with a standardized meal. The fractional absorption at 4 h (F_{c240}) after oral intake of strontium, co-ingested with a meal, appeared to be the best parameter to apply in a simple test for measuring intestinal calcium absorption using stable strontium as a marker.

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