**Biokinetic Measurements and Modeling of Urinary Excretion of Cerium Citrate in Humans**

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ABSTRACT

Studies of tracerkinetics in healthy human volunteers applying stable isotopes of cerium citrate were performed with the aim of obtaining biokinetic human data for the urinary excretion of cerium. These data were used to compare and validate the biokinetic model for lanthanides (cerium) proposed by Taylor and Leggett which is primarily based on animal data. In the present study, fourteen adults were investigated by simultaneous intravenous and/or oral administration of two cerium tracers.The cerium concentrations in urine were determined by inductively coupled plasma mass spectrometry. Ingested cerium was poorly absorbed and its low excretion values were similar to the prediction of the biokinetic model of Taylor and Leggett. However, after injection of cerium citrate into the blood its urinary excretion was rapidly increased, and the model underestimated the experimental results. The comparison between human data and model prediction implies that the urinary excretion of cerium may be dependent on the administered chemical form of cerium (speciation).

INTRODUCTION

The aim of the present work was to obtain a set of experimental human data assessing the urinary excretion of cerium (Ce) after administration of the two stable isotopes 136Ce and 138Ce as Ce citrate complex.

Cerium from the series of lanthanides has a wide application in industry, agriculture and medicine; environmental tobacco smoke and especially the use of Ce as diesel fuel additive are important sources of air pollution and could cause an increased risk of exposure to cerium in humans by inhalation of fine particles.[1-3](#_ENREF_1) The daily intake of Ce is mainly by ingestion of food and varied between 0.3 and 35 µg d-1, also higher intake values of 83-145 µg d-1 were found.[4-6](#_ENREF_4)

Besides stable isotopes of cerium (136Ce, 138Ce, 140Ce, 142Ce) two important radioactive isotopes, i.e. 141Ce (t1/2 = 32.5 d) and 144Ce (t1/2 = 284 d), occur as nuclear fission products; their principal sources are fuel reprocessing, nuclear weapon tests and accidental releases. Therefore, cerium may cause a potential radiological risk after incorporation of its radionuclides into the human body.[7](#_ENREF_7), [8](#_ENREF_8)

The International Commission on Radiological Protection (ICRP) has developed a mathematical compartment model for the lanthanides which is applied also to cerium and describes its uptake, distribution and excretion in the human body.[9](#_ENREF_9), [10](#_ENREF_10) A realistic biokinetic model of cerium is a prerequisite to correctly estimate the internal dose after incorporation of radiocerium in humans. The biokinetic model for cerium recommended by the ICRP has been revised by Taylor and Leggett;[11-13](#_ENREF_11) their improved model could be applied for estimating dose coefficients and reference bioassay data and will appear by 2017 as announced in the Occupational Intakes of Radionuclides Series of ICRP.[14](#_ENREF_14) However, all models described above were mainly derived from animal data and from the biokinetic behavior of chemical analogues, like trivalent actinides.[15](#_ENREF_15) Consequently, the developed biokinetic models can only be applied to humans with a limited reliability; therefore, more studies and information on humans are of importance to provide more realistic estimates of biokinetic models and interpretation of bioassay measurements in possibly contaminated subjects.

An overview of the results obtained from human urine measurements will be presented and compared to the prediction of the Taylor and Leggett model. The original idea to measure the 136Ce and 138Ce isotope concentrations in urine by application of thermal ionization mass spectrometry (TIMS) had to be rejected as the known interferences from barium (Ba) in the samples could not be eliminated in spite of intensive sample purification.[16](#_ENREF_16), [17](#_ENREF_17) Therefore, cooperation with the analytical platform Central Inorganic Analytics was started to analyze the urine samples by measuring the natural cerium concentration at m/z 140 via inductively coupled plasma sector field mass spectrometry (ICP-SF-MS). Since the relative abundances of the isotope 140 are substantial in all Ce tracers used (Table 1), it was expected that the presence of tracers will modify the concentrations of Ce in the urine samples.

EXPERIMENTAL SECTION

Biokinetic investigations

In the years 2007 to 2010, a human study was undertaken with the aim of investigating the intestinal absorption, systemic kinetics and urinary excretion of cerium in healthy human volunteers. The study was based on the use of stable isotopes of cerium as tracers and was performed according to the protocol approved by the Ethical Committee of the Technical University Munich, Germany. Written consent was obtained from the volunteers before each investigation.

The use of isotopically enriched stable tracers represented an ethically acceptable methodology for performing biokinetic investigations in healthy human volunteers without exposing them to an undue radiation exposure as in the case of radiotracers. Through the administration of the tracers to the volunteers and the determination of their concentrations in blood plasma and urine, it is possible to obtain information about their absorption into the systemic circulation, clearance from the blood and urinary elimination. The methodology for conducting these biokinetic studies by using two isotopically enriched stable tracers of cerium (Table 1) and the preparation of the tracer solutions were presented elsewhere.[16](#_ENREF_16) Briefly, the double tracer study consisted of a simultaneous intravenous administration of 1 µg 138Ce tracer and an oral administration of 100 µg 136Ce tracer to the human volunteers. The applied cerium tracers were administered as cerium citrate complexes. Thereafter, urine was collected after a defined time schedule. In order to follow the course of the urinary excretion of cerium over several days, samples of urine were collected up to 144 hours. Urine in the first day after administration of the stable cerium tracers was generally collected as three 4-h samples and one 12-h sample, and the following days as 24-h samples.

All urine samples were stored frozen until analysis. After thawing, the urine samples (1 mL aliquots) were transferred into closed quartz vessels and digested with HNO3, suprapure, subboiling distilled (Merck, Darmstadt) in a Seif digestion system (Seif, Unterschleißheim). The resulting solution was filled up exactly to 5 mL with Milli-Q H2O and was then ready for element determination.

**Table 1. Isotopic composition of the cerium tracers administered in the double tracer test compared to natural cerium.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Relative isotope abundances (atom%) | | | |
| Type | 136Ce | 138Ce | 140Ce | 142Ce |
| oral 136Ce tracer | 30.6 | 0.7 | 64.2 | 4.5 |
| intravenous 138Ce tracer | 0.04 | 41.6 | 55.81 | 2.55 |
| natural cerium | 0.185 | 0.25 | 88.45 | 11.11 |

Inductively coupled plasma sector field mass spectrometry

A high-resolution inductively coupled plasma sector field mass spectrometry (ICP-SF-MS) model ELEMENT II (Finnigan MAT, now Thermo Electron, Bremen, Germany) was used for the determination of cerium. The isotopes 136Ce, 138Ce, 140Ce and 142Ce were monitored. However, according to the known barium interference at isotope masses 136 and 138, which cannot be resolved even in the high resolution mode of the instrument and according to the Ba concentration in urine being 30-100-fold higher than typical Ce concentrations, the measured values from these isotopes had to be discarded. Results from 140Ce and 142Ce however were not interfered and in accordance. Sample introduction was carried out by a ESI Fast system (Elemental Scientific, Rohnert Parc, CA, USA), connected to a micromist nebulizer with a cyclon spray chamber. The RF power was set to 1300 W, the plasma gas was 15L Ar min-1, whereas the nebulizer gas was usually 0.8L Ar min-1after daily optimization. The calibration was carried out with a natural cerium standard solution (from SPEX). The measurement uncertainty was ≤ 5%.

Biokinetic modeling

The biokinetic model proposed by Taylor and Leggett was implemented in the SAAM II computer program.[18](#_ENREF_18) The transfer coefficients (per day) in the systemic model for cerium were taken from Leggett.[13](#_ENREF_13) To simulate the human experiments, performed in the clinic, 1 µg Ce for the intravenous injection, and 100 µg Ce for the simultaneous ingestion, respectively, was added. Additionally, the compartments of mouth (oral cavity contents) and oesophagus (fast and slow) of the human alimentary tract model (HATM)[19](#_ENREF_19) were connected to the systemic biokinetic model (Scheme 1); the compartments of e.g. teeth, oral mucosa or all walls were not considered. The transfer coefficients describing the movement of alimentary tract contents between the regions mouth and small intestine were accepted from HATM; thereby, data for non-caloric liquids were considered. All transfer coefficients used were listed in Table 2. After solving each model (simulating ingestion and injection) the predictions of the two model curves were added together for comparison with the data of the human double tracer study.



Scheme 1. Schematic presentation of the Taylor and Leggett model[13](#_ENREF_13) connected to the human alimentary tract model (HATM)[19](#_ENREF_19) for predicting the behavior of cerium in the human body.

**Table 2. Transfer coefficients *k* (d-1) taken from the Taylor and Leggett model**[**13**](#_ENREF_13) **and from the human alimentary tract model (HATM).**[**19**](#_ENREF_19)

|  |  |  |
| --- | --- | --- |
| from | to | *k* (d-1) |
| Blood | Liver 1 | 11.645 |
| Blood | ST 0 | 9.981 |
| Blood | ST 1 | 1.852 |
| Blood | ST 2 | 0.466 |
| Blood | Cortical surface | 3.494 |
| Blood | Trabecular surface | 3.494 |
| Blood | Kidneys 1 | 0.349 |
| Blood | Kidneys 2 | 0.117 |
| Blood | Upper large intestine | 1.397 |
| Blood | Urinary bladder content | 0.466 |
| Blood | Gonads | 0.00535a |
| Liver 2 | Blood | 0.00095 |
| Liver 1 | SI content | 0.00231 |
| Liver 1 | Liver 2 | 0.0208 |
| ST 0 | Blood | 1.386 |
| ST 1 | Blood | 0.0019 |
| ST 2 | Blood | 0.000128 |
| Cortical marrow | Blood | 0.0076 |
| Cortical surface | Cortical marrow | 0.0000821 |
| Cortical surface | Cortical volume | 0.0000411 |
| Cortical volume | Cortical marrow | 0.0000821 |
| Trabecular marrow | Blood | 0.0076 |
| Trabecular surface | Trabecular marrow | 0.000493 |
| Trabecular surface | Trabecular volume | 0.000247 |
| Trabecular volume | Trabecular marrow | 0.000493 |
| Kidneys 1 | Urinary bladder content | 0.099 |
| Kidneys 2 | Blood | 0.00139 |
| Mouth (liquids) | Oesophagus | 43,200 |
| Oesophagus (fast) | Stomach | 17,280 |
| Oesophagus (slow) | Stomach | 2880 |
| Stomach (non-caloric) | SI | 48 |
| SI content | Blood | 0.0030015b |
| SI | Right colon | 6 |
| Right colon | Left colon | 1.75c |
| Left colon | Rectosigmoid | 1.75c |
| Rectosigmoid | Feces | 1.75c |

amean value of 0.00815 (for testis) and 0.00256 (for ovaries), bbased on transfer of 6 d-1 from SI contents to right colon[19](#_ENREF_19) and on absorption factor of 0.0005[13](#_ENREF_13), cmean value of 2 (for adult male) and 1.5 (for adult female). ST stands for soft tissue, SI for small intestine.

RESULTS AND DISCUSSION

The urine samples of a set of 16 healthy volunteers (7 females, 9 males, age ranges 21-62 years) participating in the cerium tracer study were analyzed. Of these, four subjects had only received an oral dose of cerium, and ten both cerium tracers. Before tracer application, blank urines for control data were analyzed. Additionally, two volunteers collected their urines by drinking the same oral aqueous citrate solution but without addition of cerium.

Generally, the normal daily cerium concentration in urine of control subjects (without or before administration of cerium citrate) is low. Many measurement values were at the

quantification limit and varied between <5 ng/L and 61 ng/L. Similar cerium concentrations of <0.7 – 58.8 ng/L in human urine samples were found elsewhere.[20](#_ENREF_20) In our experiments, the normal daily Ce concentration in urine amounted to a mean ± SD value of 30.6 ± 9.3 ng/d, leading to a maximum of about 40 ng/d.

Ingestion

The urinary excretion course of cerium after a single oral administration of a 136Ce citrate complex is shown in Figure 1. The measured excretion values, besides individual outliers, were within the range of those of control subjects. In addition, the figure presents the predicted model curve of Taylor and Leggett simulating the cerium ingestion. For better comparison, the plotted model curve started not at zero but at the mean baseline of the control value. It is evident that the model prediction is not distinguishable from the control values and thus corresponded quite well to the human experimental data (or vice versa).



**Figure 1.** Excretion values of Ce after oral administration of 100 µg Ce citrate to four human volunteers (different black and white symbols); range of daily cerium concentration in control urines (gray-shaded area) with mean baseline of controls (dash-dotted line); urinary cerium excretion according to the Taylor and Leggett model (solid line) with absorption factor (f1 value) of 5 x 10-4 and a single cerium ingestion of 100 µg.

In this respect, our results may be due to the assumed low gastro-intestinal absorption factor (f1) of 5 x 10-4 for cerium.[13](#_ENREF_13) Considering an f1 of 5 x 10-4 and an oral intake of 100 µg Ce, only 50 ng Ce would be absorbed into the blood. This amount would not significantly increase the normal basal cerium concentration in the blood plasma. A study with German and Spanish breast feeding mothers showed cerium concentrations in their blood plasma between <10–70 ng/L.[21](#_ENREF_21) Taking into account, for example, a blood plasma volume of 3.5 liter for a 70 kg human subject, an additional uptake of 50 ng Ce would not become important. Hence, the daily urinary excretion of cerium after ingestion of cerium citrate remained unchanged compared to controls. Thus, our experimental results do not appear to contradict the assumed f1 value of 5 x 10-4.

Injection

Figure 2 presents the data showing the daily urinary excretion pattern of cerium when administered as cerium citrate both orally and intravenously to ten human volunteers. The excretion in all human subjects varied partly over a wide range, probably due to individual differences. In contrast to the study with the oral tracer alone (Figure 1), the measured values after double tracer administration were far above the natural Ce excretion. The initial peak differed significantly to the baseline. The urinary excretion of incorporated cerium took place mostly in the first eight hours indicating a very fast excretion process. After one day most of the incorporated cerium was eliminated and the excretion rates were negligible reaching normal basal values.



**Figure 2**. Urinary excretion of Ce after ingestion of 100 µg Ce citrate and simultaneous injection of 1 µg Ce citrate in humans (black and white symbols); median value of the experiments (dashed line); model prediction according to Taylor and Leggett (solid line), and mean baseline of daily cerium concentration in control urines (dash-dotted line).

It has to be pointed out that the measured 140Ce concentrations in principle can consist of the initial Ce body burden with natural isotope ratio and of the applied tracers, which were isotopically enriched with 136Ce or 138Ce. For the latter ones the 140Ce determination underestimates the total Ce concentration in urine. A precise quantification of the Ce concentrations thus was impossible since 136Ce and 138Ce were not measurable due to Ba interferences; and the isotopic composition of cerium in urine, originating from isotopic tracers and/or probably also from natural body load in various amounts, was not known. However, since the observed sudden increase of Ce concentration and subsequent return to baseline directly follows the application of tracers, it might be assumed that most of excreted Ce is derived from this tracer application. For estimating lower and upper limits of excreted Ce concentrations, calculations should assume separately the sole responses to the different tracers and to natural body burden: assuming a sole response to the 136Ce tracer (with 140Ce abundance at 64.2% compared to 88.45% natural abundance) the excretion maximum would be underestimated by a factor of 1.38 (88.45/64.2). When assuming a sole response to the 138Ce tracer the excretion maximum is underestimated by a factor of 1.58 (88.45/55.8) whereas assumption of only natural body burden would need no correction of measured values. The actual result will lie in between the highest and lowest calculated ranges. But, finally, the shape of the Ce excretion curve was crucial for our comparison with the Taylor and Leggett model.

According to the Taylor and Leggett model the main cerium excretion is also within the first few hours. Here, the peak as well asstarting at the baselineshowed that the model prediction lies above the excretion values of the controls but the rise was not as high. The Taylor and Leggett model describes a lower systemic elimination via the urinary pathway and underestimated the real situation in humans regarding the urinary excretion of cerium by at least a factor of 2. The comparison between the experimental human data and model prediction indicates that the urinary excretion of cerium may be dependent on the administered chemical form of cerium (speciation). The model cannot distinguish between different cerium species, and their subsequent metabolic pathway.

Indeed, the elimination of cerium from blood seems to be strongly dependent on the chemical form of administration. Aeberhardt[22](#_ENREF_22) showed in his study with rats a differential behavior of cerium depending on whether the cerium was injected as ionic or colloidal form; and the urinary excretion seemed to be negligible, amounting only to 1-3% of the injected dose. The authors mentioned a study from Durbin[23](#_ENREF_23) who reported a higher excretion rate of Ce citrate in animals.

It is known that lanthanides show a strong tendency to hydrolyze in solution;[24](#_ENREF_24) therefore in metabolic studies lanthanides should be introduced in a chemical form which is stable enough to e.g. prevent precipitation in blood. In our human study the cerium tracers were administered as cerium citrate complex. Citrate forms with cerium mainly (Ce(citrate)2)3- species under nearly neutral conditions. Chemically, this cerium citrate complex is quite stable with a formation constant of log beta2 of about 11.2.[25](#_ENREF_25) As a consequence, cerium might be excreted via the urinary route as a non-dissociated complex and the excretion rate of the cerium citrate complex could be higher than e.g. the excretion of a pure ionic Ce salt*.* Probably, cerium in an ionic form or in a less chemically complexed complex will be hydrolyzed or complexed with other endogenous ligands when entering the blood leading to a low renal clearance; and other elimination pathways, e.g. the biliary route, might come into consideration.

A study describing the metabolic fate of blood citrate in rats after intravenous administration of radioactive citrate showed a rapid turnover of blood citrate.[26](#_ENREF_26) Within a period of 3h up to 90% of the radioactivity was recovered in the urine and mainly present in the carboxyl groups of the urinary citrate. It can be assumed that in our human study the excretion of cerium, which was administered highly complexed with citrate, followed the fast excretion of citrate.

Interestingly, similar results in humans[27](#_ENREF_27) were presented regarding the kinetics of ruthenium (Ru); in this study, after an injection of a highly complexed Ru citrate tracer the urinary excretion of Ru was faster than the renal elimination of a lower complexed Ru salt. In this context, Veronese[28](#_ENREF_28) already indicated the importance of speciation in biokinetic studies and in the modelling process.

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**Author Contributions**

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

**Notes**

The authors declare no competing financial interest.

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