Strontium as a Marker for Intestinal Calcium Absorption: The Stimulatory Effect of Calcitriol

Marieke Dijkgraaf-ten Bolscher,1* J. Coen Netelenbos,1 Rob Barto,2 and Wim J.F. van der Vijgh2

Background: Intestinal strontium absorption is becoming accepted as a clinical and diagnostic tool for assessing intestinal calcium absorption in humans. However, little is known about whether intestinal strontium absorption, like that of calcium, is stimulated by calcitriol in healthy humans.

Methods: The effect of calcitriol on intestinal strontium absorption was measured in eight healthy men, ages 20–60 years. Before administration of calcitriol, two tests were performed with an interval of 10 days for calculating the within-subject variation (SEr). Before the third test, 0.5 mg of calcitriol was given twice daily for 3 days. In each test, the fractional strontium absorption (Fc240) and the area under the concentration-time curve (AUC0–240) 4 h after an oral strontium load of 2.5 mmol were calculated.

Results: The within-subject SEr of Fc240 and AUC0–240 was 1.7 ± 0.7 and 0.83 ± 0.1, respectively. The stimulatory effect of calcitriol on Fc240 and AUC0–240 was 35% (21.8 ± 2.0 to 28.8 ± 2.4; P = 0.003) and 61% (8.97 ± 0.97 to 14.4 ± 1.3 mmol · L−1 · min; P = 0.001), respectively.

Conclusions: Although the reproducibility of AUC0–240 and its sensitivity to calcitriol were better than those of Fc240, the Fc240 of strontium is preferred for a clinical test because of its simplicity, requiring only two instead of five blood samples.

© 2000 American Association for Clinical Chemistry

Abnormal or inadequate intestinal calcium absorption is a contributing factor in certain disease states, e.g., osteoporosis. The study of intestinal calcium absorption and calcium metabolism in animals and humans is essential for further elucidating basic mechanisms, for understanding disease processes, and for assessing therapeutic strategies.

Strontium has become a clinical and diagnostic tool for measuring calcium absorption in humans (1–6). Various studies have demonstrated a close correlation between the intestinal absorption of (radioactive) calcium and nonradioactive strontium (7, 8). Previously, we determined the bioavailability (AUCpo/AUCiv × Doseiv/Dosepo) of SrCl2 in healthy male volunteers to obtain a simple parameter that is most representative for intestinal absorption. We found that the bioavailability of SrCl2 correlated best with the fractional absorption of strontium at 240 min (Fc240) after the oral intake of the test solution (1). Using this test, we undertook a double-blind placebo-controlled study to investigate whether 17β-estradiol stimulates intestinal strontium absorption in healthy postmenopausal women (9). In that study, 17β-estradiol did not affect the Fc240 of strontium after the test solution was ingested. A possible explanation could be that the calcium/strontium load (9.0 mmol of calcium and 5.0 mmol of strontium) given to the women was too high, which could render the test insensitive with respect to the possible stimulation of active transport by 17β-estradiol. Therefore, we reduced the load of the test to 2.5 mmol of strontium only.

The aim of this study was to assess the reproducibility of the renewed strontium absorption test. Thereafter, the stimulatory effect of calcitriol [1,25(OH)2D3] on intestinal strontium absorption, as reflected by Fc240, was investigated. To check for possible shifts in the absorption profile, plasma strontium concentrations at 1, 2, and 3 h were also determined.

Materials and Methods

STUDY POPULATION

Eight healthy male volunteers, ages 20–60 years, participated in this study. All subjects gave informed consent to participate in the study. The ethics committee of our
hospital approved the study. All procedures followed were in accordance with the Declaration of Helsinki. The mean body weight of the volunteers was 74.9 kg (range, 55–90 kg); their mean body mass index was 23.8 kg/m² (range, 20.2–25.9 kg/m²).

STUDY DESIGN

All subjects arrived in the outpatient clinic after overnight fasting. Body weight was measured, and blood samples were withdrawn for the determination of plasma strontium, calcium, albumin, phosphate and 1,25(OH)₂D. Subjects received 200 mL of a test solution containing 2.5 mmol of SrCl₂ without additional calcium. The test solution was consumed within 1 min. One, 2, 3, and 4 h thereafter, a blood sample was withdrawn for the determination of strontium. Blood samples were centrifuged at 1500g for 10 min. Subsequently, plasma was separated and stored at −20 °C until analysis. All plasma samples were analyzed for strontium by graphite furnace atomic absorption spectrophotometry (10). The SrCl₂ solution was prepared by the Pharmacy Department of our hospital. SrCl₂·6H₂O (pro analysis) was obtained from Merck.

The reproducibility of the strontium absorption test was assessed by repeating the test with an interval of 10 days. Seven days after the second baseline test, participants received 0.5 mg of 1,25(OH)₂D₃ (Rocaltrol; Roche Nederland) twice daily for 3 days before the third strontium absorption test.

METHODS

Plasma 1,25(OH)₂D was measured by radioimmunoassay after immunoextraction (IDS). The intra- and interassay coefficients of variation (CVs) were 6.3% and 9.7%, respectively.

DATA ANALYSIS

For each subject, three plasma strontium concentration-time curves were obtained. All concentrations measured were corrected for endogenous strontium concentrations, determined at t = 0 of each test. The time at which the highest plasma concentration (cₘₐₓ) was observed was designated tₘₐₓ. The area under the concentration-time curve up to time t (AUC⁰⁻ᵗ), expressed as mmol·L⁻¹·min⁻¹, was calculated by the trapezoidal rule, using the pharmacokinetic computer program Topfit 2.0 (11). The Fc of strontium 4 h after an oral strontium load (Fc₂₄₀) was calculated according to the following formula (1):

\[
Fc_{240} (\%) = \left( \frac{c_{240} - c_0}{D} \times V \right) \times 100
\]

in which \( c_{240} \) is the plasma concentration 4 h after ingestion (mmol/L); \( c_0 \) is the plasma concentration at 0 min (mmol/L); \( V \) is the central volume of distribution, represented by 15% of the body weight (L); and \( D \) is the dose of strontium (2.5 mmol).

The within-subject variation of Fc₂₄₀ was determined from its values in test 1 (baseline, \( x_{i1} \)) and test 2 (replicated test, \( x_{i2} \)) by the equation:

\[
SE_R = \sqrt{\frac{\sum_{i=1}^{n} (x_{i1} - x_{i2})^2}{2n}}
\]

in which \( n \) represents the number of volunteers (n = 8).

STATISTICAL ANALYSIS

Data are expressed as the mean (± SE). Between- and within-subject variations were assessed for Fc₂₄₀ and AUC⁰⁻₂₄₀. The significance of the stimulatory effect of
1,25(OH)2D3 on intestinal strontium absorption (Fc240 and AUC0–240) between baseline and treatment test was determined by a paired-sample t-test. The correlation between the plasma 1,25(OH)2D concentration and the values of Fc240 and AUC0–240 at baseline and after treatment with 1,25(OH)2D3 were tested for significance by means of a Spearman correlation test. Differences were significant at P < 0.05 (two-tailed). All analyses were performed using the Statistical Package for the Social Sciences (SPSS 7.5 for Windows).

Results

The plasma concentration-time curves of strontium at baseline and after 1,25(OH)2D3 treatment of each subject are shown in Fig. 1. After oral administration of the test solution, the mean maximum plasma strontium concentration of the baseline test was 51.9 ± 5.0 μmol/L (range, 25.4–69.3 μmol/L; n = 8). This maximum concentration (cmax) was reached at a mean time (tmax) of 173 min (range, 120–240 min) after administration.

The within- and between-subject variation of Fc240 and AUC0–240 are shown in Table 1. The within-subject variation (SEw) of the AUC0–240 was approximately twofold lower than that of the Fc240 (0.83 ± 0.1 and 1.7 ± 0.7, respectively).

The biochemical variables (Table 2) did not show a significant change after treatment with 0.5 μg of 1,25(OH)2D3 twice daily for 3 days in these eight volunteers. Despite a nonsignificant increase of the plasma 1,25(OH)2D concentration, 1,25(OH)2D3 significantly increased the AUC0–240 of strontium (Table 3).

The stimulatory effect of 1,25(OH)2D3 on Fc240 and AUC0–240 was 35% (21.8% to 28.8%) and the mean value of tmax decreased to 128 min (range, 60–240 min).

Discussion

As expected, reducing the load of the strontium absorption test to 2.5 mmol of strontium only, instead of 9.0 mmol of calcium and 5.0 mmol of strontium, produced an increased value of Fc240, i.e., from 7.0% to 21.8%. The within-subject variation for Fc240 of strontium was considerably better than that described earlier (1, 7). Furthermore, the CV for AUC0–240 was 10%, which is quite similar to the CV of 11.8% reported by Vezzoli et al. (3), who used a comparable strontium load of 30.2 μmol/kg. The mean AUC0–240 values of strontium of 9.36 (baseline) and 8.58 (repeated test) mmol·L⁻¹·min in our present study were comparable with the 8.0 and 9.43 mmol·L⁻¹·min found by Vezzoli and co-workers (3, 4) in two separate studies.

The stimulating effect of 1,25(OH)2D3 on intestinal calcium absorption has already been well established (13, 14). With regard to strontium, different opinions exist about the mechanism of strontium transport through the intestinal wall. Dumont et al. (15) have concluded from their experiments that transport of strontium is passive only. Others have found evidence for active intestinal strontium absorption and indications for a common transport mechanism of calcium and strontium (16, 17). Our previous studies in rats gave evidence for active transport of strontium across the intestinal wall, which was 1,25(OH)2D3 dependent (18). To apply strontium as a marker for intestinal calcium absorption in humans, it is necessary that the effect of intervention on intestinal calcium absorption is reflected by the strontium absorption test.

1,25(OH)2D3 stimulated intestinal strontium absorption by increasing the cmax as illustrated in Fig. 1; tmax also decreased. This means that strontium, like calcium, is at least partially absorbed by active transport. To date, only one study in humans has discussed the stimulatory effect of 1,25(OH)2D3 on intestinal strontium absorption (19). However, the authors determined fractional strontium absorption by means of deconvolution, for which purpose 45Ca was given orally and 85Sr was administered intrave-

---

**Table 1. Between- and within-subject variation of the fractional absorption (Fc240) and area under the concentration-time curve (AUC0–240) of strontium 4 h after an oral load of 2.5 mmol of SrCl2 in eight healthy male volunteers.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Replicated test</th>
<th>Between-subject</th>
<th>Within-subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fc240, %D</td>
<td>21.8 (2.0)</td>
<td>20.9 (2.3)</td>
<td>21.4 (2.0)</td>
</tr>
<tr>
<td>AUC0–240, mmol·L⁻¹·min</td>
<td>9.36 (0.97)</td>
<td>8.58 (1.0)</td>
<td>8.97 (0.97)</td>
</tr>
</tbody>
</table>

* Values are mean (SE).

---

**Table 2. Effect of 1,25(OH)2D3 on biochemical variables.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>1,25(OH)2D3 treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium, mmol/L</td>
<td>2.26 (0.02)</td>
<td>2.29 (0.02)</td>
<td>0.19</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>46.8 (0.89)</td>
<td>47 (0.65)</td>
<td>0.69</td>
</tr>
<tr>
<td>Phosphate, mmol/L</td>
<td>1.12 (0.05)</td>
<td>1.21 (0.07)</td>
<td>0.06</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>99.6 (2.5)</td>
<td>102 (3.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>1,25(OH)2D3, pmol/L</td>
<td>80 (7.9)</td>
<td>93 (7.1)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

* Values are mean (SE).
nously. This procedure is debatable because the two elements have comparable, but not identical, pharmacokinetic behaviors.

Our present study measured intestinal strontium absorption and shows that strontium, like calcium, can be stimulated by 1,25(OH)2D3. Because of its good reproducibility, it is a sensitive test. It can be concluded, therefore, that the strontium absorption test provides an appropriate measure for intestinal calcium absorption and that this test is a good alternative for measuring modulating effects of interventions on intestinal calcium absorption as discussed recently by Heaney (20).

The Fc240 can be used for the assessment of intestinal strontium absorption after limited sampling. Fc240 did not correlate with plasma 1,25(OH)2D concentrations. A possible explanation for this finding is that the tmax is not always near 240 min. Nevertheless, the Fc240 of strontium was still highly significantly increased after 1,25(OH)2D3 treatment. Therefore, the Fc240 of strontium can still be used as a measure for intestinal calcium absorption. However, when more information is desired about possible changes in the absorption profile, the concentration-time curve of strontium must be considered. Under these circumstances, quantitative information can then be obtained by the measurement of an absorption parameter that is based on more than two samples, e.g., AUC0–240.

The present study supports the view that the strontium absorption test is a good measure for intestinal calcium absorption. Although the reproducibility of the AUC0–240 and its sensitivity to 1,25(OH)2D3 were better than those of Fc240, the Fc240 of strontium is preferred as a clinical test because of its simplicity, requiring only two instead of five blood samples.

We thank Simone Neele for collecting the numerous blood samples. The volunteers are acknowledged for their enthusiastic participation in this study. We thank the Laboratory of Clinical Chemistry and the Laboratory of Endocrinology, University Hospital Vrije Universiteit, Amsterdam, for the measurement of the biochemical variables and the Department of Pharmacy for preparing the test solution. We also thank J. Kuik for advice concerning the statistical analysis.

References


