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No difference in intestinal strontium absorption after oral or IV calcitriol in children with secondary hyperparathyroidism

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No difference in intestinal strontium absorption after oral or IV calcitriol in children with secondary hyperparathyroidism.

Background. Oral and intravenous calcitriol bolus therapy are both recommended for the treatment of secondary hyperparathyroidism, but it has been claimed that the latter is less likely to induce absorptive hypercalcemia. The present study was undertaken to verify whether intravenous calcitriol actually stimulates intestinal calcium absorption less than oral calcitriol and whether it is superior in suppressing parathyroid hormone (PTH) secretion.

Methods. Twenty children (16 males, age range of 5.1 to 16.9 years, mean creatinine clearance 21.9 ± 11.5 mL/min/1.73 m^2, range of 7.4 to 52.7) with chronic renal failure (CRF) and secondary hyperparathyroidism [median intact PTH (iPTH), 327 pg/mL; range 143 to 1323] received two single calcitriol boli (1.5 mg/m^2 body surface area) orally and intravenously using a randomized crossover design. iPTH and $1,25(OH)_2D_3$ levels were measured over 72 hours, and intestinal calcium absorption was measured 24 hours after the calcitriol bolus using stable strontium (Sr) as a surrogate marker. Baseline control values for Sr absorption were obtained in a separate group of children with CRF of similar severity.

Results. The peak serum level of $1,25(OH)_2D_3$ and area under the curve baseline to 72 hours ($AUC_{0–72h}$) were significantly higher after intravenous (IV) calcitriol ($AUC_{0–72h}$ oral, 1399 ± 979 pg/mL · hour vs. IV 2793 ± 1102 pg/mL · hour, $P < 0.01$), but the mean intestinal Sr absorption was not different [$SrAUC_{0–240\ min}$ during the 4 hours after Sr administration 2867 ± 1101 FAD% (fraction of the absorbed dose) vs. 3117 ± 1581 FAD% with oral and IV calcitriol, respectively]. The calcitriol-stimulated Sr absorption was more then 30% higher compared with control values (2165 ± 176 FAD%). A significant decrease in plasma iPTH was noted 12 hours after the administration of the calcitriol bolus, which was maintained for up to 72 hours without any differences regarding the two routes of administration.

Conclusions. These results demonstrate that under acute conditions, intravenous and oral calcitriol boli equally stimulate calcium absorption and had a similar efficacy in suppressing PTH secretion.

Secondary hyperparathyroidism remains a significant therapeutic problem in patients with chronic renal failure (CRF) [1, 2], particularly in children who are susceptible to a rapid appearance of skeletal deformities and stunting [3]. Calcitriol is considered to be an important part of the standard treatment of secondary hyperparathyroidism. It lowers parathyroid hormone (PTH) secretion by increasing the serum calcium concentration and by decreasing the expression of pre-pro-PTH mRNA [4–6]. It also suppresses parathyroid cell proliferation [7], thus preventing parathyroid gland hyperplasia [7, 8]. A single dose of calcitriol results in a prolonged suppression of PTH mRNA [4] and a prolonged decrease of plasma intact PTH (iPTH) in patients [9, 10]. Intravenous calcitriol bolus therapy [11] given one to three times per week has been proposed as the treatment of choice. The efficacy of this treatment modality has been ascribed to the high peak concentration of calcitriol, which may saturate the calcitriol receptor completely. Several clinical studies have proven the efficacy of intravenous (IV) bolus therapy [12, 13]. However, not only IV bolus therapy but also intramuscular [14] and oral bolus therapies [15–17] have been shown to be effective. The clinical use of calcitriol is limited by hypercalcemia and hyperphosphatemia, and it has been claimed that this risk is decreased with the use of IV calcitriol [18] because of the avoidance

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Key words: vitamin D, $1,25(OH)_2D_3$, intact PTH, calcium absorption, hypercalcemia, parathyroid hormone, skeletal deformities in children, chronic renal failure.

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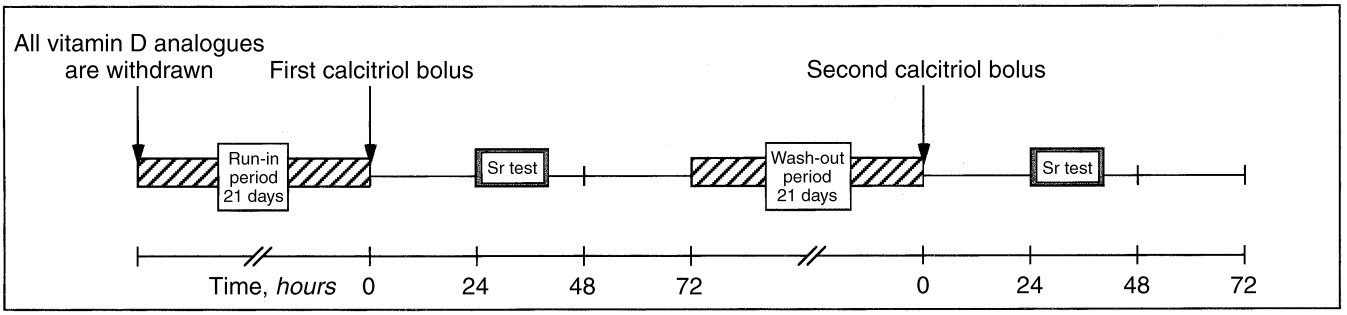

Fig. 1. Study design (Sr test, strontium absorption test).

of any direct contact between calcitriol and mucosal epithelial cells during the process of intestinal absorption. The efficacy and safety of intravenous and oral bolus therapy have been compared in uncontrolled and head-on comparison studies [16, 18, 19], but no definite conclusions can be drawn from these studies regarding differential effects on calcium absorption and the consequent risk of hypercalcemia.

The present study was designed to compare the effects of a single oral and IV calcitriol bolus on plasma iPTH levels and on the intestinal calcium absorption of children and adolescents with secondary hyperparathyroidism. Stable strontium (Sr) was used as a surrogate marker for calcium [20–24].

METHODS

Patients

Twenty patients were recruited from eight pediatric nephrology units. The entry criteria included an age between 5 and 18 years and a creatinine clearance (according to Schwartz) of less than 60 mL/min/1.73 m^2 body surface area (BSA). The exclusion criteria were renal replacement therapy, primary metabolic disease, acute illness, organ (other than kidney) disease, gastrointestinal malabsorption, and endocrine disorders (such as hypoparathyroidism, diabetes mellitus, hypothyroidism, and hypopituitarism). In addition, any patient with hypocalcemia and hypercalcemia (serum calcium <8.5 and >11.0 mg/dL), hyperphosphatemia, or hypophosphatemia (serum phosphate <3.5 or >7.0 mg/dL), uncorrected acidosis (serum bicarbonate < 18 mmol/L) were also considered ineligible for the study. A total of 20 patients (16 males) successfully completed the entire protocol. Their mean age was 13.1 ± 3.3 years (range 5.1 to 16.9), and they had a mean creatinine clearance value of 21.9 ± 11.5 mL/min/1.73 m^2 (range 7.4 to 52.7). The underlying diseases leading to CRF were obstructive uropathy (N = 10), renal hypodisplasia (N = 5), polycystic kidney disease (N = 2), nephrophthisis (N = 2), and Alport syndrome (N = 1).

Baseline control Sr absorption without calcitriol was measured in five additional children with CRF using identical inclusion criteria for selection. These patients had a mean age of 13.4 ± 3.1 years, and a mean creatinine clearance of 31.5 ± 16.5 mL/min/1.73 m^2.

Study protocol

Study design. The study was designed as a multicenter, prospective, stratified and randomized study with a crossover design for treatment modalities: (*1*) an initial three-week run-in (washout) period; (*2*) the first calcitriol bolus given orally or intravenously (according to the randomization schedule); (*3*) a second washout period of three weeks; and (*4*) the second IV or oral calcitriol bolus (Fig. 1). The group of patients recruited for the baseline control Sr test underwent a run-in period, at the end of which the Sr test was performed without administering calcitriol.

The study protocol was approved by the Ethics Committee of the University of Heidelberg (Germany) and by local ethics committees. Signed informed consent was obtained from the parents.

Run-in period. At the beginning of the run-in period, all of the vitamin D preparations were discontinued, whereas the usual medications (including phosphate binders) were regularly administered according to individual requirements (mean daily calcium carbonate supplementation was 29.1 ± 41.5 mg/kg). All patients received instructions to restrict their dietary phosphate intake and were advised to keep a constant self-selected diet throughout the duration of the study. At the end of the run-in period, the patients with iPTH values twice above the upper normal limit were stratified and randomized; if iPTH was still below this target limit, the run-in period was continued for a further three weeks (which was necessary for one patient only).

Study procedure. All study patients were stratified on the basis of their plasma iPTH levels and were then randomized to one of the two treatment sequences. The stratification criteria were (*1*) iPTH 3 times and (*2*) >3

times the upper normal limit. Using the restricted randomization technique, the patients were assigned to receive two calcitriol boli: oral calcitriol first, followed by IV calcitriol ($N = 10$) or IV calcitriol followed by oral calcitriol ($N = 10$). A washout period of three weeks was placed between the administration of the first and the second bolus.

The study and control patients were admitted to the hospital, and after an overnight fast, blood was drawn for baseline biochemical determinations. Calcitriol (1.5 μg/m^2 BSA) was administered only to study patients either orally or intravenously with Rocaltrol® capsules (0.25 to 0.5 μg; Hoffman-La Roche, Basel, Switzerland) and Calcijex® vials (1 μg/mL; Abbott Labs, Abbott Park, IL, USA). The oral dose of calcitriol was rounded to the nearest multiple of 0.25 μg. Precisely the same amount was used for the intravenous administration. The patients were not allowed to ingest food for the first four hours following calcitriol administration.

Twenty-four hours after calcitriol administration, the intestinal Sr absorption test was performed. The Sr test was performed without administering any calcitriol in the patients who underwent the baseline control Sr test.

Washout period. During the three weeks between the first and the second calcitriol bolus, all vitamin D analogues were withheld, whereas all other medications were regularly administered as during the run-in period.

Biochemical determinations. Before the administration of both the first and the second bolus, baseline laboratory determinations were made for serum creatinine, calcium, phosphate, alkaline phosphatase, albumin, bicarbonate, $1,25(OH)_2D_3$, and plasma iPTH. Serum calcium, phosphate, $1,25(OH)_2D_3$, and plasma iPTH were also determined 1, 2, 3, 4, 6, 12, 24, 48, and 72 hours after calcitriol administration [in the case of the IV bolus, serum $1,25(OH)_2D_3$ was also measured 5 minutes after the injection].

Intestinal strontium absorption test. The Sr absorption test was performed according to Reid et al [20, 24]. A blood sample (2 mL of whole blood) was drawn for baseline Sr determination. Then the standard dose of hexahydrated Sr chloride (8.06 mg/kg body weight, equivalent to 2.65 mg of $SrCl_2$) was administered per os in 200 mL of deionized water to be drunk in one minute. Thereafter, blood was drawn for Sr determination at 30, 60, 90, 120, 180, and 240 minutes. Between blood samplings, the vascular access was maintained with 0.9% saline solution (heparinized catheter). The subjects were not allowed to eat any food during the four hours of the Sr absorption test.

Strontium was measured using an atomic absorption spectrophotometer (4000 Atomic Absorption; Perkin Elmer, Norwalk, CT, USA), previously calibrated with a Sr solution of known concentration. The procedure involved stabilization of the air-acetylene flame temperature for 10 minutes, calibration of the equipment, analysis of the samples, and reading of the values at a wavelength of 460.7 nm (slit 0.7). All samples from each subject were processed and analyzed in duplicate in the same assay. The reproducibility of the method was evaluated on 60 samples re-analyzed on different days. The coefficient of variance (CV) at our laboratory was 4.1%.

The Sr concentration is reported as the fraction of the absorbed dose (FAD%) contained in the extracellular fluids, assuming that this was 15% of ideal body weight, according to the following formula [20]:

$$\text{FAD} = \frac{[\text{Sr}] \times 15\% \text{ of ideal body weight}}{\text{Sr administered dose}}$$

The areas under the curve were calculated by means of the trapezoidal method (Bezout integral).

Analytical methods

The levels of serum calcium, phosphate, $1,25(OH)_2D_3$ and Sr, and plasma iPTH were centrally determined; the remaining laboratory determinations were made locally.

Serum calcium and phosphate were measured using an automated Hitachi analyzer. Serum $1,25(OH)_2D_3$ was determined by a radio receptor assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) with mean intra-assay and interassay coefficients of variations of 7.8 and 13.7%, respectively. The normal range was 18 to 62 pg/mL. The plasma iPTH was measured in duplicate using a two-site IRMA (Allegro Intact PTH kit; Nichols Institute Diagnostics). The assay had a sensitivity of 1 pg/mL, and the duplicate measurements showed a mean intra-assay CV of 4.1%. The mean interassay CV was 5.8%.

Statistical analysis

Baseline descriptive variables are given as mean and standard deviation, and data for $1,25(OH)_2D_3$, Sr, and PTH are presented as least square means and standard error.

For all variables, the Shapiro-Wilk's test for normality was used [25]. Student's *t*-test for unpaired data was used for evaluating baseline values for Sr, calcium, phosphate, iPTH, and $1,25(OH)_2D_3$. Statistical analysis was performed by means of the general linear model for repeated measures, split-plot design (SAS/PC, release 6.04; SAS Institute, Cary, NC, USA). For all variables, the sequence effect was tested to investigate whether the two sequences of treatment produced different responses (validity of crossover design) [26]. The period and treatment effect (treatment = period sequence) were analyzed with multivariate tests. Nonorthogonal multiple comparisons were tested using the Scheffés test [27]. All the tests were two tailed, and the type 1 error level was set at 5%.

Table 1. Biochemical findings in children with secondary hyperparathyroidism before the administration of an oral or intravenous (IV) calcitriol bolus

	Oral	IV	*P*
C_{Cr} *mL/min/1.73 m²*	21.7 ± 12.0	21.6 ± 12.0	NS
Serum albumin *mg/dL*	4.6 ± 0.6	4.7 ± 0.5	NS
Serum bicarbonate *mEq/L*	23.0 ± 3.3	21.9 ± 4.0	NS
Serum calcium *mg/dL*	10.0 ± 1.0	10.0 ± 0.8	NS
Serum phosphate *mg/dL*	5.7 ± 1.6	5.6 ± 1.2	NS
Serum alkaline phosphatase *IU/mL*	373 (63–1126)[a]	407 (53–1104)[a]	NS
Intact PTH *pg/mL*	327 (102–1707)[a]	305 (143–2419)[a]	NS
$1,25(OH)_2D_3$ *pg/mL*	24.7 ± 11.5	22.8 ± 11.5	NS

Data are given as mean ± standard deviation or [a]median and range. C_{Cr} is creatinine clearance.

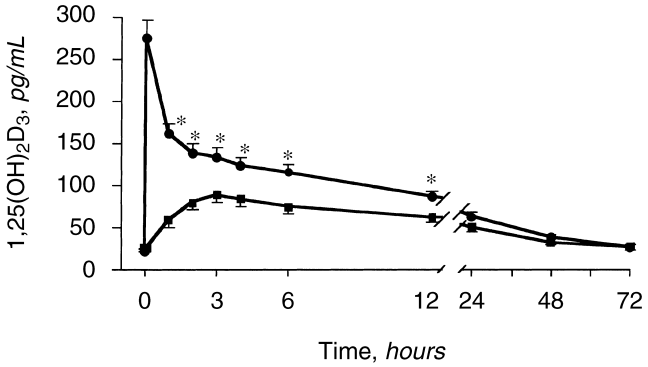

Fig. 2. Time course of $1,25(OH)_2D_3$ serum concentration following a calcitriol bolus (1.5 μg/m²) given orally (■) or intravenously (●). For intravenous calcitriol, an additional determination was performed five minutes after calcitriol injection (mean ± SEM, $*P < 0.01$).

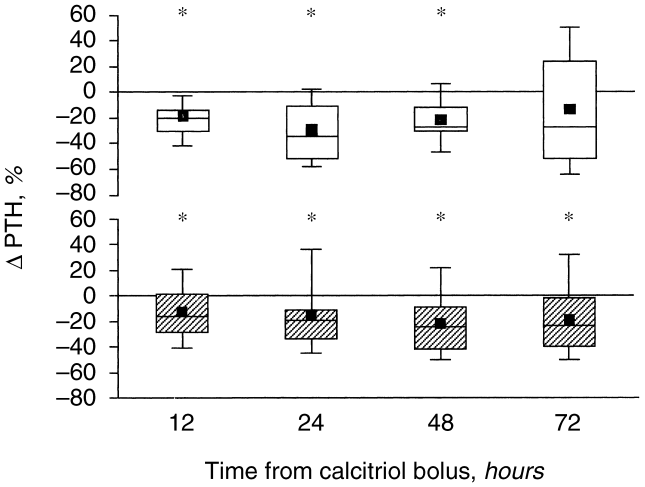

Fig. 3. Box plot of the percentage decrease from baseline of intact parathyroid hormone (iPTH) after a bolus of calcitriol (1.5 μg/m²) given orally (□) and intravenously (▨). $*P < 0.05$.

RESULTS

Baseline biochemistry

At the end of the control period, preceding stratification and randomization, the following laboratory findings were obtained: mean serum creatinine 4.75 ± 2.5 mg/dL, calcium 10.1 ± 0.91 mg/dL, phosphate 5.4 ± 1.1 mg/dL, $1,25(OH)_2D_3$ 22.8 ± 12.5 pg/mL, median iPTH 327 pg/mL (range of 143 to 1323 pg/mL). Table 1 shows the laboratory findings immediately before the oral and IV calcitriol bolus administrations. Patients who underwent the baseline Sr test (without calcitriol) had the following biochemical findings: mean serum creatinine 4.3 ± 1.7 mg/dL, calcium 9.4 ± 0.48 mg/dL, phosphate 5.1 ± 0.93 mg/dL; $1,25(OH)_2D_3$ 19.8 ± 9.7 pg/mL; and median iPTH 201 pg/mL (range of 89 to 429 pg/mL).

Effect of calcitriol on serum biochemistry

As expected, the time course of serum $1,25(OH)_2D_3$ after oral and IV calcitriol administration was substantially different (Fig. 2), with the IV route leading to significantly higher peak serum concentrations (282 ± 90 vs. 94 ± 36 pg/mL, $P < 0.0001$) and a higher $1,25(OH)_2D_3$ $AUC_{0\text{–}72h}$ (4321 ± 1446 vs. 3180 ± 1096 pg/mL · h; $P < 0.01$). Peak serum $1,25(OH)_2D_3$ levels following oral administration typically occurred after two to fours hours (mode 3 hours); furthermore, serum $1,25(OH)_2D_3$ concentrations remained persistently and significantly lower after oral than after IV administration for up to 12 hours. Serum $1,25(OH)_2D_3$ levels returned to their baseline values after 72 hours.

No significant decrease in plasma iPTH concentrations was observed during the first six hours after calcitriol administration, but they were significantly lower than at baseline after 12 hours and remained so for up to 72 hours (Fig. 3). However, this decrease was not significantly different after oral and IV bolus administration, although the maximum percentage decrease from baseline (nadir) was significantly greater after oral administration (−46.1 ± 14.8% vs. −34.3 ± 22.1%, $P < 0.05$).

The results were not different when patients with high and moderately elevated iPTH plasma levels were analyzed separately. There was also no correlation between iPTH values at the start and the percentage decrease following calcitriol bolus.

Neither the oral nor the IV bolus had any significant effect on the serum concentration of calcium and phosphate during the 72 hours following their administration (data not given).

Effect of calcitriol on intestinal Sr absorption

As shown in Figure 4, the mean Sr absorption following IV or oral calcitriol was more than 30% higher compared with control values. However, the Sr absorption was similar after the IV and oral calcitriol bolus, the results being substantially the same whether the absorption was analyzed in terms of Sr peak concentrations or

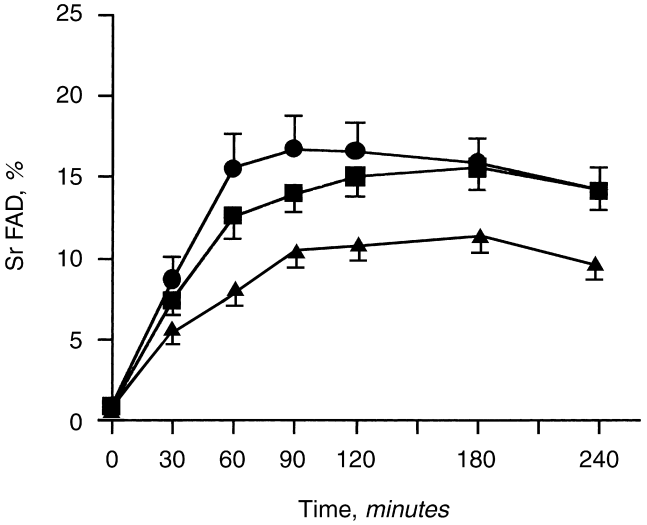

Fig. 4. Time course of Sr fractional absorption without calcitriol (▲) and 24 hours after a calcitriol bolus (1.5 μg/m²) given orally (■) and intravenously (○) in children with secondary hyperparathyroidism (mean ± SEM).

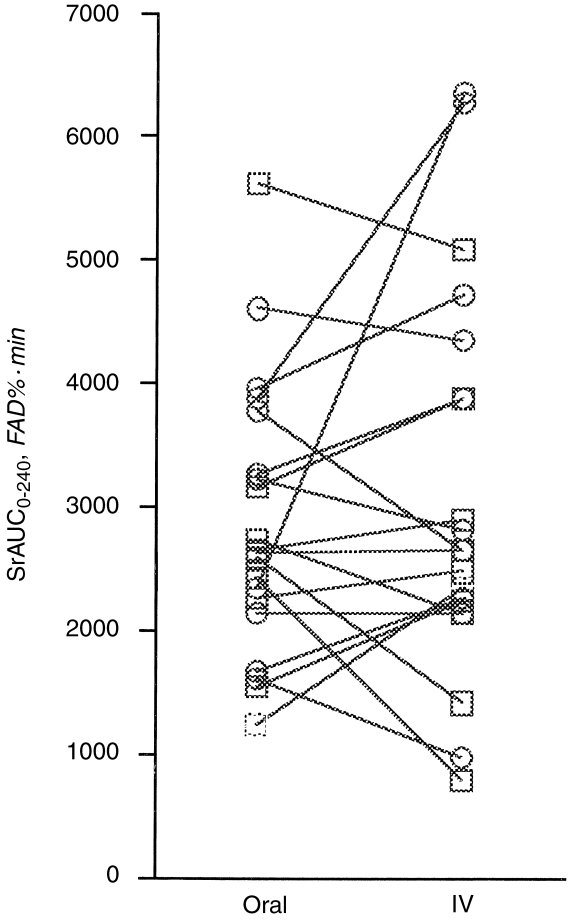

Fig. 5. Individual $SrAUC_{0-240\,min}$ following the administration of an oral and an IV calcitriol bolus. Symbols indicate the patient's order of calcitriol administration: oral followed by intravenous (□); intravenous followed by oral (○).

the $SrAUC_{0-240\,min}$. The Sr peak concentrations without calcitriol and after oral and IV administration were 12.6 ± 1.5, 17.5 ± 6.31, and 18.7 ± 9.25 FAD%, respectively, and the $SrAUC_{0-240\,min}$ values were 2165 ± 176, 2867 ± 1101, and 3117 ± 1581 FAD% · min. The individual results of $SrAUC_{0-240\,min}$ in patients are depicted in Figure 5. The results were not different when the analysis was done separately for patients with high and moderately elevated iPTH levels (data not given).

As shown in Figure 6A, the $SrAUC_{0-240\,min}$ after an oral bolus of calcitriol significantly correlated with creatinine clearance; no correlation was observed after IV calcitriol (Fig. 6B).

DISCUSSION

The present study in children with CRF gives clear evidence that intestinal calcium absorption measured by stable Sr, as a surrogate marker for calcium, is not significantly different after a single calcitriol oral or IV bolus. Furthermore, it shows that plasma iPTH levels become significantly lower 12 hours after the calcitriol bolus and remain low for up to 72 hours regardless of the route of administration.

Intravenous calcitriol bolus therapy has been recommended for the control of secondary renal hyperparathyroidism since 1984 [11]. One advantage that has been claimed is the avoidance of any direct contact between intestinal epithelial cells and calcitriol during the intestinal absorption process, thus reducing the risk of hypercalcemia [11, 12]. Indeed, the results of some clinical trials have led to the conclusion that the IV route of administration is associated with fewer episodes of hypercalcemia [13]. However, all studies comparing IV and oral calcitriol [16–19] do not allow definite conclusions to be drawn, since the calcitriol dose and the amount of prescribed phosphate binders were not fixed, and/or the patients were not adequately randomized in terms of dialysis modality and/or the degree of hyperparathyroidism. Furthermore, in these studies, hypercalcemia may have occurred not only as a result of intestinal calcium absorption, but also (and even primarily) as a consequence of low bone turnover caused by calcitriol therapy. The present crossover study was designed to measure intestinal calcium absorption following a single oral or IV bolus of calcitriol given to the same patients.

We used stable Sr as a surrogate calcium marker for the measurement of intestinal calcium absorption. This method is safe and suitable for repeated measurements (particularly in children). It was first described by Reid et al, who demonstrated a very close correlation between Sr and calcium absorption ($r = 0.93$) co-measured using ^{45}Ca [20]. The fractional absorption of Sr was lower in

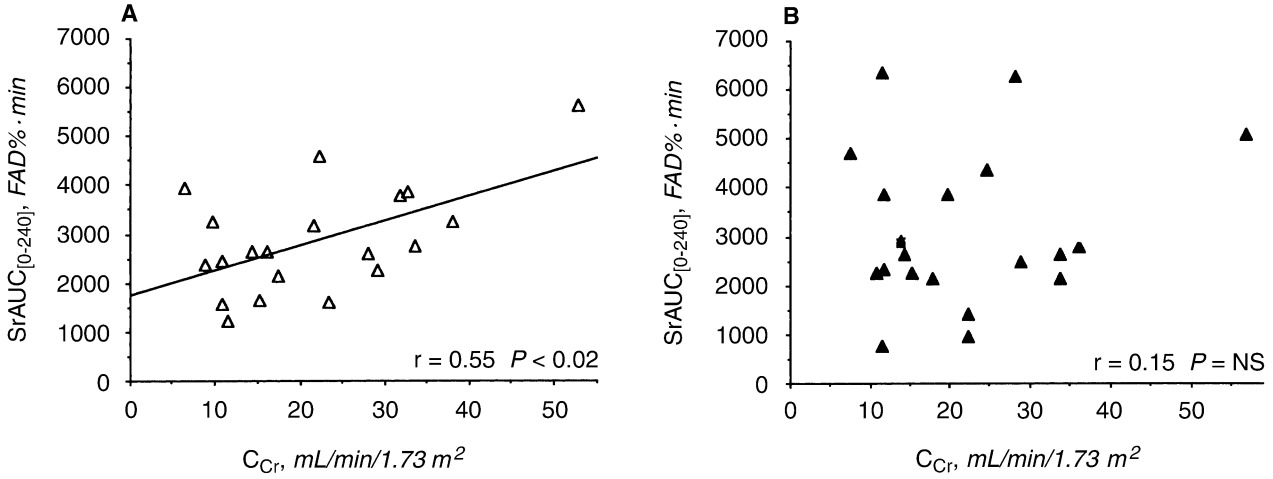

Fig. 6. Relationship between creatinine clearance (C_{Cr}) and Sr intestinal absorption measured 24 hours after an oral (A) and an intravenous (B) calcitriol bolus. $SrAUC_{0\text{-}240\,min}$ is the area under the Sr fractional absorption time curve.

absolute terms than that of ^{45}Ca, but the time course very closely resembles that of radioactive calcium. Recently, we [24] and many others [20–23] have shown that the Sr test is an easy, highly reproducible, and reliable method for estimating the intestinal absorption of calcium in healthy volunteers and in patients with CRF [28].

In the present study, Sr absorption was measured 24 hours after the bolus administration of calcitriol on the basis of the following considerations: $1,25(OH)_2D_3$ influences the intestinal calcium absorption by rapid nongenomic actions on the cellular membrane [29–31] and by activating a specific transport system mainly in the duodenum [32], which involves gene activation and protein synthesis (genomic effect) [33–35]. In calcium-deprived and vitamin D-depleted rats, the calcium transport response to a single injection of calcitriol is biphasic [29]: The early response is characterized by a relatively rapid rise to a peak at six hours followed by a rapid decline. The second or late response becomes apparent approximately 12 hours after administration, reaches a peak at 24 hours, and maintains this level for at least 72 hours. In vitamin D-repleted animals, rapid nongenomic action of $1,25(OH)_2D_3$ (transcaltachia) developed within a few minutes [30]. In our previous studies on healthy volunteers, no early effect of a calcitriol bolus (1.5 $\mu g/m^2$ as used in the present study) on Sr absorption could be detected, whereas Sr absorption significantly increased by 35% after 24 hours [24].

In the present study of children with CRF, the mean Sr absorption following calcitriol administration was about one third higher than control values, indicating the efficacy of calcitriol treatment. However, mean basal values for healthy adults [24] were not reached. There was no difference with the oral or IV administration of calcitriol. One might argue that the results have been influenced by differential effects of the IV or oral calcitriol bolus on renal Sr excretion. Although we did not measure this effect, they are not relevant since Sr absorption was measured for only four hours following its administration. The renal loss within this time is very small, and we believe it can be neglected for the calculation of FAD. Our results also showed that Sr absorption following an oral calcitriol bolus was significantly correlated with creatinine clearance. Studies in adults with CRF have demonstrated that intestinal calcium absorption decreases with the progression of renal failure and the decrease in serum calcitriol concentration [36, 37].

Our study extends these findings by demonstrating that the correlation between glomerular filtration rate and Sr absorption remained after an oral dose of calcitriol, thus showing an increasing insensitivity to calcitriol with decreasing renal function. It is of interest to note that no correlation between creatinine clearance and Sr absorption was observed when calcitriol was administered as an IV bolus, because Sr absorption fell within the normal range despite a low filtration rate (at least in a subgroup of patients).

The second important result of the present study is the finding that a single bolus of calcitriol can lower plasma iPTH levels for up to 72 hours. This confirms our previous observations in children [10] and adults [9] and extends these with the notion that the time course and magnitude of iPTH suppression are not influenced by the route of calcitriol administration. With the limitations of the method used, we did not see any systematic change in serum calcium and phosphate levels during the entire study period.

The effect of calcitriol on iPTH was noted only 12 hours after the first administration, thus pointing to a genomic effect. We have likewise demonstrated by means of decon-

volution analysis in healthy volunteers that intravenous calcitriol has no "early" (nongenomic) effects on pulsatile and tonic PTH secretion, whereas both were significantly decreased after prolonged calcitriol administration [38]. This prolonged decrease in iPTH is in agreement with the prolonged decrease in mRNA for pre-pro-PTH after the injection of a calcitriol bolus in rats [4, 39].

The effects of intravenous calcitriol have been related to (*1*) higher peak concentrations and greater occupancy of the vitamin D receptor, and (*2*) modulation and up-regulation of the vitamin D receptor [40]. The present study and the clinical experience that oral bolus calcitriol therapy is highly effective and even equi-effective in head-on comparison studies [16, 19] suggest that the intermittent modality of administration rather than the peak concentration of calcitriol is responsible for the efficacy of intravenous treatment.

Our study was performed as an acute short-term study comparing the effects of a single oral calcitriol bolus versus a single IV calcitriol bolus. The question as to whether the results can be extended to repeated and prolonged application of calcitriol bolus treatment cannot be answered with certainty at this moment. Controlled clinical studies seem to confirm that IV calcitriol is not superior to oral calcitriol in suppressing iPTH levels. Based on the results of our study, it cannot be assumed that the IV calcitriol route is superior to the oral one with regard to intestinal calcium absorption.

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