Pharmacokinetics of Calcium Absorption from Two Commercial Calcium Supplements

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This study was conducted to compare pharmacokinetic indices of calcium absorption after a single oral (500 mg calcium) load of Citracal (calcium citrate) and Os-Cal (calcium carbonate). In 18 postmenopausal normal women, venous blood samples were obtained for the measurement of calcium before and hourly for 6 hours after an oral ingestion of Citracal, Os-Cal, or placebo with a breakfast meal. The change in area under the curve (ΔAUC) in serum calcium from preload was 2.5-fold greater for Citracal than Os-Cal, and the peak-basal variation in serum calcium was 76% higher for Citracal than Os-Cal. The increment in serum calcium from preload after Citracal administration was significantly higher than that obtained after placebo load during most time periods and significantly higher than that of Os-Cal at 1, 4, and 5 hours after load. In contrast, ΔAUC and peak basal variation of Os-Cal did not differ significantly from placebo, and increment in serum calcium was significantly increased from placebo only at 6 hours. In conclusion, Citracal is much more bioavailable than Os-Cal.

Journal of Clinical Pharmacology, 1999;39:1151-1154

Calcium supplements are widely used for the prevention of osteoporosis.[1] To subserve this purpose, many calcium preparations are available in the marketplace. Most of these preparations are composed of calcium carbonate or calcium citrate. While many studies have compared calcium absorption from these salts,[2,3] few studies have examined the bioavailability of commercial calcium preparations.

This problem is due to the difficulty in measuring calcium absorption from already formulated tablet preparations of calcium supplements. Reliable techniques based on radioactive or stable calcium isotopes[2] cannot be applied because the labeling of calcium salts must be undertaken before making them into tablets. Calcium absorption from tablet formulations may be measured with the calciuric response to oral calcium load.[3,4] However, this test lacks sensitivity when used at the customary dose of 500 mg calcium and may be influenced by variable renal function and fluctuation in baseline calcium excretion before the calcium load.[4]

Ironically, classic pharmacologic approaches based on changes in serum calcium concentration have not been applied. In this communication, we compared area under the curve, peak to basal variation, and time to reach peak in serum calcium following a single oral dose of 500 mg calcium as two popular calcium supplements, Citracal (calcium citrate) and Os-Cal (calcium carbonate).

MATERIALS AND METHODS

Patient Data

Eighteen normal women participated in the study (mean age = 61.5 years, range = 45 to 80 years). All were postmenopausal. Two were Hispanic, and 16 were white. They were ambulatory and free of hyperparathyroidism, hypercalcemia, thyroid excess, intestinal malabsorption, chronic diarrheal conditions, kidney stones, or liver disease. They were not taking bisphosphonate, fluoride, calcitonin, steroids, diuretics, or anticonvulsants. Their endogenous creatinine clearance was greater than 50 ml/min. The protocol was approved by the Institutional Review Board of the

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University of Texas Southwestern Medical Center. Written informed consent was obtained before the study began.

Study Protocol

In this crossover study, subjects underwent three phases of study, the order of which was randomized. For 1 week prior to each phase, they were instructed to be maintained at home on a diet restricted in calcium (400 mg/day) and sodium (100 meq/day).

The day following 1 week of instructed diet represented the test day for each phase. The subjects ingested ample amounts of distilled water at bedtime of the day prior to the test day and throughout the test day. At 8 a.m. of the test day, a standard breakfast was ingested comprising 20 g farina, 10 g cane sugar, 1 fresh egg, 49 g bread, and 200 ml decaffeinated coffee. At 8 a.m., an oral load of one of test medications was given.

In one phase, subjects ingested as a single dose 500 mg calcium as Citracal (two tablets of Citracal containing 250 mg calcium per tablet, specially formulated by Mission Pharmacal Company, San Antonio, TX). In another phase, subjects took a single dose of Os-Cal (one tablet containing 500 mg calcium, marketed by SmithKline Beecham Consumer Healthcare, Pittsburgh, PA). In the third phase, two placebo tablets prepared by Mission to be identical in appearance to Citracal tablets were taken.

On the test day of each phase, venous blood was obtained at 8 a.m. before the test load and hourly thereafter until 2 p.m. (corresponding to 1-6 hours after dosing). Serum sampling was inadvertently omitted at 5 and 6 hours after dosing for all three phases in the first 4 patients. In the remaining 14 patients, a full sampling for 6 hours was done during all three phases. Lunch was withheld. Serum samples were analyzed for calcium by atomic absorption spectrophotometry.

Initial pilot study as well as published data[5] indicated that the rise in serum calcium concentration after oral calcium load is gradual. Moreover, it was impractical to continue the study beyond 6 hours after calcium dosing since few subjects would agree to abstain from ingesting lunch beyond that period. These considerations led to the adoption of the simplified sampling scheme, comprising hourly samples for 6 hours, as described above.

Statistical Analysis

The following pharmacokinetic measures were obtained from each load study: (1) increment in serum calcium concentration from baseline (preload) at 1 to 6 hours postload, (2) change in area under the curve (ΔAUC) or increment in serum calcium over the duration of study (4 or 6 hours postload), (3) peak-basal variation (difference between peak serum calcium concentration postload and preload value), and (4) t_{max}, or time in hours postload when the peak increment in serum calcium concentration was attained. For all these measures, multiple comparisons between phases were made with Bonferroni-adjusted paired *t*-tests. The significance level for this multiple comparison was considered to be 0.0167.

RESULTS

Increment in Serum Calcium from Baseline

The increment in serum calcium concentration from preload over 6 hours after load is shown in Figure 1. After placebo load, there was a little or no change in serum calcium concentration. Following Os-Cal load, serum calcium concentration increased slightly; it was significantly greater than that of the placebo group only at 6 hours. In contrast, the increment in serum calcium concentration following Citracal load was significantly higher than that of the placebo load at every hour postload, except at 1 hour. Moreover, the increment in serum calcium for Citracal was significantly greater than that of Os-Cal at 1, 4, and 5 hours.

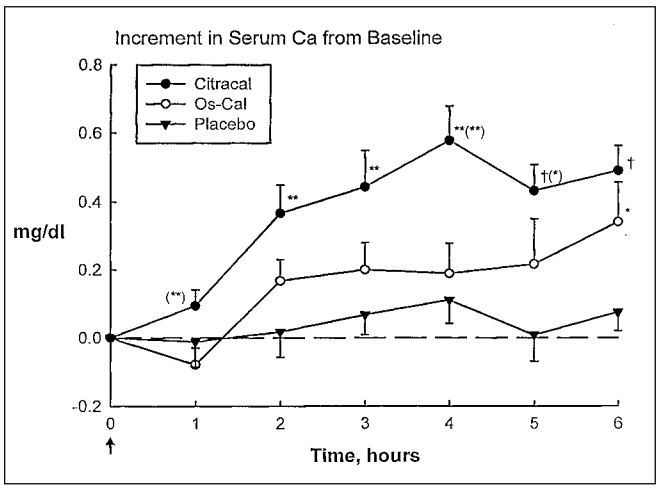

*Figure 1. Increment in serum calcium from preload over 6 hours after an oral load of Citracal (500 mg calcium as calcium citrate), Os-Cal (500 mg calcium as calcium carbonate), or placebo. The arrow on the x-axis indicates zero time when a load was delivered. Vertical bars indicate standard error of the mean. Significant difference between placebo and Os-Cal or Citracal is shown by *p < 0.05, **p < 0.0167, and †p < 0.001. Symbols within parentheses indicate significant difference between Citracal and Os-Cal.*

Table I Comparison of Pharmacokinetic Parameters between Citracal, Os-Cal, and Placebo

	Citracal	Os-Cal	Placebo
ΔAUC, mg Ca•4-6 h/dl	1.82 ± 0.25†(**)	0.72 ± 0.37	0.19 ± 0.24
Peak-basal variation in serum calcium, mg/dl	0.67 ± 0.10**(**)	0.38 ± 0.08	0.27 ± 0.06
t_{max}, h	4.44 ± 0.27**	3.89 ± 0.36	3.34 ± 0.35

Numbers are presented as mean ± *SD*. Significant difference between placebo and Citracal is shown by $**p < 0.0167$ and $\dagger p < 0.001$. Significant difference between Citracal and Os-Cal is represented by (**). No significant difference was found between Os-Cal and placebo.

Pharmacokinetic Parameters

ΔAUC of serum calcium after placebo load was negligible (Table I). Compared with placebo, ΔAUC of Os-Cal was not significantly changed but that of Citracal was significantly higher. ΔAUC of Citracal was significantly greater than that of Os-Cal by about 2.5-fold.

The peak-basal variation in serum calcium after placebo load was modest at 0.27 mg/dl (Table I). Compared with placebo, the peak-basal variation of Os-Cal was not significantly altered, but the value for Citracal was significantly higher. The peak-basal variation in serum calcium of Citracal was significantly greater than that of Os-Cal by 76% (0.67 mg/dl vs. 0.38 mg/dl).

The peak increment in serum calcium was reached in 3.34 hours after the placebo load (Table I); t_{max} was not significantly different from placebo after Os-Cal load, but it increased significantly from placebo following Citracal load.

DISCUSSION

In this study, calcium absorption from two popular calcium supplements given with a meal was compared by using a classic pharmacokinetic approach.

It was shown that ΔAUC, peak-basal variation, and t_{max} of serum calcium after Os-Cal load (calcium carbonate, 500 mg calcium) did not differ significantly from placebo. Increment in serum calcium after Os-Cal load was significantly higher than after placebo load only at 6 hours. In contrast, ΔAUC, peak-basal variation, and t_{max} of Citracal were significantly higher than those of placebo. Moreover, the increment in serum calcium after Citracal load was significantly higher than that of placebo during most time periods. Compared with Os-Cal, Citracal gave a 2.5-fold higher ΔAUC and 76% greater peak-basal variation in serum calcium. The results suggest that Citracal is more bioavailable than Os-Cal.

Practical constraints prevented us from blood sampling beyond 6 hours. We did not provide lunch because we feared that it might alter serum calcium concentration. We felt that most subjects would be unwilling to abstain from ingesting lunch beyond 6 hours from the breakfast meal. The increment in serum calcium from baseline at 6 hours after calcium loads was still substantial, indicating that calcium absorption had not been completed. Thus, we were not able to measure maximum ΔAUC or $t_{1/2}$ of decline from peak. Though "abbreviated," this pharmacokinetic study should still be adequate in assessing relative bioavailability of two calcium preparations.

It has been suggested that the calcemic response to calcium citrate load might be exaggerated because of complexation of calcium in circulation by the absorbed citrate.[6] This possibility is unlikely since the rise in serum citrate concentration after the oral load of soluble citrate is negligible.[7] Moreover, past studies have revealed that the rise in total serum calcium following calcium citrate load is associated with a commensurate rise in serum-ionized calcium and is an appropriate physiological response of parathyroid suppression.[5] It has also been alleged that calcium citrate enjoys a superior bioavailability compared with calcium carbonate when salts are administered on an empty stomach[3,4] but not when provided with meals.[2] This study indicates that the improved bioavailability of calcium citrate over calcium carbonate is independent of interaction with meals.

In an ongoing study, we are pursuing a detailed examination of Citracal and Os-Cal by measuring not only calcemic response as described here but also calciuric response, serum-ionized calcium, parathyroid hormone, and citrate and calcium citrate complexes.

In summary, Citracal overall is 2.5-fold better absorbed than Os-Cal when given with meals. Moreover, Citracal produces a higher peak calcium concentration in serum compared with Os-Cal. Our ongoing study should shed further light on the physiologic and clinical relevance of this finding.

The authors would like to thank John Poindexter for expert data management. We thank Mission Pharmacal Company for providing Citracal and placebo. Authors do not own equity or serve as a consultant in Mission or SmithKline Beecham. No direct research grant was received from either company.

REFERENCES

1. Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, et al: A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med* 1990;323:878-883.

2. Recker RR: Calcium absorption and achlorhydria. *N Engl J Med* 1985;313:70-73.

3. Harvey JA, Zobitz MM, Pak CYC: Dose dependency of calcium absorption: a comparison of calcium carbonate and calcium citrate. *J Bone Miner Res* 1988;3:253-258.

4. Nicar MJ, Pak CYC: Calcium bioavailability from calcium carbonate and calcium citrate. *J Clin Endocrinol Metab* 1985;61:391-393.

5. Gonelli S, Cepollaro C, Camoreale A, Nardi P, et al: Acute biochemical variations induced by two different calcium salts in healthy perimenopausal women. *Calcif Tissue Int* 1995;57:175-177.

6. Heaney RP, Dowell MS, Barger-Lux MJ: Absorption of calcium as the carbonate and citrate salts, with some observations on method. *Osteop Int* 1999;9:19-23.

7. Pak CYC, Skurla C, Brinkey L, Sakhaee K: Augmentation of renal citrate excretion by oral potassium citrate administration: time course, dose frequency schedule, and dose-response relationship. *J Clin Pharm* 1984;24:19-26.