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Relative Bioavailability of Calcium from Calcium Formate, Calcium Citrate and Calcium Carbonate

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Running title: Calcium Absorption from Calcium Formate

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Abbreviations used: ΔC_{max}, maximum increment in serum calcium concentration; AUC, area under the plasma concentration-time curve; ΔAUC, increment in area under the concentration-time curve; iPTH, intact parathyroid hormone 1-84; t_{max}, the time at which the maximum change occurred

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Abstract

Calcium is an essential nutrient required in substantial amounts but many diets are deficient in calcium making supplementation necessary or desirable. The objective of this study was to compare the oral bioavailability of calcium from calcium formate, a new experimental dietary calcium supplement, to that of calcium citrate and calcium carbonate. In a four-way crossover study either a placebo or 1200 mg calcium as calcium carbonate, calcium citrate or calcium formate were administered orally to 14 healthy adult female volunteers who had fasted overnight. After calcium carbonate the maximum rise in serum calcium (ca. 4%), and the fall in serum iPTH (ca. 20-40%), did not differ significantly from placebo. After calcium citrate the changes were modestly but significantly ($p < 0.05$) greater, but only at times 135-270 min after ingestion. In contast, within 60 min after calcium formate serum calcium rose by ca. 15% and serum iPTH fell by 70%. The mean increment in AUC (0-270 min) for serum calcium after calcium formate (378 mg•min/dL) was double that for calcium citrate (178 mg•min/dL; $p < 0.01$), while the latter was only modestly greater than either placebo (107; $p < 0.05$) or calcium carbonate (91; $p < 0.05$). In this study calcium formate was clearly superior to both calcium carbonate and calcium citrate in ability to deliver calcium to the bloodstream after oral administration. Calcium formate may thus offer significant advantages as a dietary calcium supplement.

Introduction

Osteoporosis is a skeletal disorder characterized by a decrease in bone mass, compromised bone strength and an increase in bone fragility predisposing to fracture (Report, 2001). It is an important health threat in modern Western countries; in the United States alone it is estimated that 10 million persons have osteoporosis while 18 million others have low bone density placing them at risk of this disorder (Charles, 1992; Report, 2001). Many factors influence bone health but osteoporosis can be viewed as a calcium deficiency disorder in which bone is resorbed in order to maintain serum calcium levels when calcium excretion is not balanced by calcium absorption (Charles, 1992; Reginsgter et al., 1993; Martini et al., 2002). Calcium from the diet and other sources is absorbed primarily in the intestine and is the nutrient most important for attaining peak bone mass during adolescence and for preventing and treating osteoporosis (Report, 2001).

Recommendations for daily dietary calcium intake that range from 400 to 1200 mg per day depending on age and gender have been issued by governmental and non-governmental organizations in many countries (Levenson et al., 1994; Report, 2001). Because many modern diets do not provide the recommended levels of calcium, dietary calcium supplements have been recommended for prevention of osteoporosis as well as for other conditions including hypertension, hypercholesterolemia and cancer (Porter, 2003). Many forms of dietary calcium supplements are widely available, but products containing calcium carbonate and calcium citrate are the most common (Levenson et al., 1994; Heller et al., 1999; Porter, 2003). Over the past 20 years the absorption of calcium from dietary supplements has been studied by many methods. Some studies have shown the more soluble calcium citrate to be somewhat better absorbed than the relatively insoluble calcium carbonate while others have shown the opposite result and still

others have found no significant difference (Sakhaee et al., 1999; Heaney et al., 2001). The lack of consensus regarding these two important forms of calcium supplements has been atttributed in part to differences in study design (e.g. fed vs. fasted vs. achlorhydric subjects; high load vs. low load of calcium), to differences in analytical methodology (measurement of serum calcium increment vs. urinary calcium increment vs. fractional absorption via isotopic tracer or mass-balance approaches) and to genetic and other factors that differ between individuals (Sakhaee et al., 1999; Abrams, 2003).

Calcium formate is a highly soluble calcium salt containing 30.8% calcium by weight (compared to 40.0% for calcium carbonate and 24.1% for calcium citrate). The high solubility and calcium content of calcium formate suggests that it might be an efficient source of calcium for dietary supplementation (DeLuca, 2003), but no information is available concerning the bioavailability of calcium from calcium formate. The aim of this study, therefore, was to compare the relative oral bioavailability of calcium from a single dose of calcium formate to that of calcium citrate and calcium carbonate in healthy adults.

Materials and Methods

Subjects. The subjects were 14 normal, healthy adult females between 19 and 33 years of age. They were free of diabetes, hyperparathyroidism, thyroid excess or other endocrine disorder, bone disease, kidney stones, nephrolithiasis, renal disease, peptic or duodenal ulcer, bowel disease, intestinal resection or malabsorption, regional enteritis, chronic diarrheal conditions and liver disease. In addition, none of the subjects was pregnant or breastfeeding. At no time during the study or the seven days preceeding it did any of the subjects take vitamin or mineral supplements, anticonvulsants, diuretics, steroids (other than oral contraceptives), bisphosphonates (e.g. Fosamax®), or other medications that could affect calcium or vitamin D metabolism. Subjects meeting these criteria were included in the study irrespective of the timing of their menstrual cycle, information on which was not recorded. The study protocol was approved by the Institutional Review Board of the Heart of America Research Institute (Kansas City, Kansas), and signed written informed consent was obtained from each subject before the study began.

Study Design. In this four way crossover study each subject served as her own control. On four different days each subject ingested either a placebo or a single oral dose of one of three different calcium preparations. Calcium formate was administered as 6 capsules of 650 mg calcium formate (custom tableted by Opti-Med, Seymour, IN ; 1200 mg total calcium), calcium carbonate was administered as 2 tablets of Caltrate 600® (Whitehall-Robins Healthcare, Madison, NJ; 1200 mg total calcium), and calcium citrate was administered as 6 tablets of Citracal® (Mission Pharmacal, San Antonio, TX; 1200 mg total calcium). Methyl cellulose was used as the placebo (Opti-Med). On each study day, subjects arrived at the clinic prior to 8:00

am after having fasted for ca. 10 hours overnight. Between 8:00 and 9:00 am each subject ingested either a placebo or one of the three calcium compounds along with 240 mL (8 ounces) of water. During the 4.5 hours subsequent to tablet ingestion, subjects were allowed water ad lib but no other beverage or food was allowed until after the last blood sample was collected. Venous blood samples for determination of serum calcium and intact parathyroid hormone (iPTH) levels were taken immediately prior to ingestion of the placebo or calcium compound (time 0) and at 30, 60, 90, 135, 180, 225 and 270 minutes post-dose. The interval between consecutive doses (placebo or calcium compound) was at least 48 hours in all cases. The order of treatment groups was placebo, calcium formate, calcium carbonate and calcium citrate.

The bioavailability of an orally administered exogenous compound is defined as the fraction of the dose that reaches the systemic circulation. Bioavailability is often determined pharmacokinetically by comparing the dose-normalized area under the curve (AUC) for and oral vs. an intravenous dose, i.e. $F = (AUC_{po}/Dose_{po}) / (AUC_{iv}/Dose_{iv})$. For an endogenous substance such as calcium, measurement of the absolute bioavailability (fractional absorption) of an oral dose requires the use of isotopic methods (DeGrazia et al., 1965; Roth et al., 1985; Smith et al., 1985), but for assessing relative oral bioavailability the pharmacokinetic method is much more convenient (Heller et al., 1999; Heller et al., 2000; Heaney, 2001; Heaney, 2003a).

Analytical Methods. Total serum calcium concentration was quantified by forming a colored complex with arsenazo III (#588-3P, Sigma, St. Louis, MO). The absorbance of the complex at 600 nm is proportional to the concentration of calcium in the serum. The volumes of arsenazo III and serum used were twice Sigma's recommended volumes in order to provide improved accuracy and precision; the calibration range was from 5 to 15 mg/dL. Pre-analytical sources of error were minimized during collection and storage of specimens.

The concentration of intact parathyroid hormone 1-84 (iPTH) in serum was determined using an immunoradiometric assay (Diagnostic Products Corporation, Los Angeles, CA) according to the manufacturer's directions. Affinity-purified polyclonal anti-PTH (44-84) antibody is immobilized on the wall of a polystyrene tube and ^{125}I-labeled affinity-purified polyclonal anti-PTH is in the liquid phase. A sandwich complex is formed between immobilized antibody, PTH and labeled antibody. The calibration range was from 10.5 to 2571 pg/mL and the lower limit of quantitation was 10.5 pg iPTH/mL serum. In a number of instances after the administration of calcium formate, the serum level of iPTH fell below this value. Thus, to avoid problems of missing data during statistical analyses, the value of 10.5 was recorded and used in the statistical analysis whenever the actual value was at or below this level.

Pharmacokinetic Calculations. For each subject and for each treatment group, the maximum increment in serum calcium concentration (ΔC_{max}) was calculated by subtracting the zero-time (pre-dose) value from the maximum value observed post-dose. The increment in area under the curve for serum calcium (ΔAUC) was calculated using the trapezoidal rule approach, and the means and 95% confidence intervals were calculated for each of these parameters for each treatment group.

Statistical analyses. Repeated measures multivariate analysis of variance procedures, as implemented in SYSTAT 9.0 (SPSS, Inc., Chicago, IL), were performed separately on the percent of control (time 0) data for serum calcium and iPTH. Significant differences among treatments were analyzed by comparisons between pairs of treatments. Statistical significance

was defined as $p < 0.05$. Data in Table 2 are presented as means with 95% confidence intervals, and means with non-overlapping confidence intervals are considered as significantly different.

Results

Comparison of treatment groups. Figures 1 and 2 show the changes in mean serum calcium and serum iPTH concentrations, respectively, following oral administration of 1200 mg calcium as either calcium formate, calcium carbonate or calcium citrate, compared to placebo. Among the four treatment groups there were no significant differences in the pre-dose (zero-time) values for either serum calcium or serum iPTH. However, significant post-dose differences between the treatment groups were found for both serum calcium and serum iPTH concentrations by means of multivariate repeated measures analysis of variance. Thus, for serum calcium concentrations, Wilk's Lambda = 0.123, $F(3,11) = 26.027$ and $p < 0.001$, while for serum iPTH Wilk's Lambda = 0.144, $F(3,11) = 21.732$ and $p < 0.001$.

Specific univariate *post hoc* comparisons between the groups are summarized in Table 1. For the calcium formate group both the serum calcium and serum iPTH concentrations clearly differ substantially and significantly from those of the other three groups at all times from 30-270 minutes post dose. While there are slight differences in serum calcium and serum iPTH concentrations between the calcium carbonate and placebo groups, the differences are not significant. There is a marginally significant main effect difference in calcium concentrations between the calcium citrate and placebo groups. Differences in iPTH between these groups did not show a significant main effect difference, but there was a significant interaction between treatment and time ($F(6,78) = 21.716$, $p < 0.001$). A further *post hoc* test showed that for all times from 135 to 270 min post dose, citrate was significanty different from placebo ($F(1,13) = 12.469$, $p = 0.004$). Individual subject data for serum calcium and iPTH were also expressed as a percentage of their respective pre-dose values and the means subjected to further analysis as described below.

Changes in serum calcium. As seen by reference to Figure 1, after placebo administration, serum calcium rose by about 5% over the baseline value during the course of the experiment. After administration of calcium carbonate, changes in serum calcium followed closely those of the placebo group; these increases probably reflect normal diurnal variations in serum calcium concentration (Nielsen et al., 1991; Vesely et al., 1996; el-Hajj Fuleihan et al., 1997). The lack of difference between the placebo and calcium carbonate groups does not necessarily mean that no calcium was absorbed from the latter; more likely it means that mechanisms that remove calcium from the bloodstream were able to keep pace with a low rate of calcium absorption and thereby prevent serum calcium from rising significantly during the absorption phase. After administration of calcium citrate, serum calcium concentrations rose slowly but steadily, reaching a plateau ca. 9% above baseline by 180 minutes post dose. At 180, 225 and 270 minutes post dose the increases following calcium citrate were significantly greater than those for the placebo ($F(1,13) = 16.508$, $p = 0.001$) or calcium carbonate ($F(1,13) = 29.094$, $p < 0.01$).

After calcium formate administration the time profile of serum calcium was strikingly different compared to the other three treatment groups. As early as 30 minutes post dose serum calcium had risen by 9%, and by 60 min it reached a plateau value about 15% above baseline that was maintained from 60 to at least 270 minutes post-dose. At all times from 30 to 270 minutes the serum calcium concentrations in the calcium formate group were significantly greater than both the zero-time values and the corresponding time value for any other treatment group. Given the normally tight regulation of serum calcium, in which absorption from dietary sources is balanced by excretion and/or storage in tissues, this dramatic rise suggests that

calcium from calcium formate is absorbed with exceptional efficiency and speed compared to calcium carbonate or calcium citrate.

Table 2 gives the pharmacokinetic parameters derived for the increments in serum calcium concentration (i.e. the changes from zero-time baseline values) observed in this study. It is important to note that even when calcium was not administered (i.e. the placebo group), serum calcium concentrations were not constant throughout the time course of the experiment (0800-1330 hours) due to expected diurnal variation. Hence, the increments in serum calcium concentration following administration of a calcium salt must be compared to the endogenous changes observed in the placebo group. Between the calcium carbonate and placebo groups there were no significant differences in any of the pharmacokinetic parameters for calcium. For the calcium citrate group the mean maximum increment, ΔCmax, was significantly greater than for the placebo or carbonate groups, but it occured relatively late at ca. 225 minutes post dosing, consistent with the slow steady rise in serum calcium observed in Figure 1. After calcium formate administration the ΔCmax and ΔAUC values were double those for calcium citrate. The large and highly significant increases in these parameters indicate that calcium from calcium formate is absorbed much more rapidly, and therefore to a much greater extent, than calcium from the other calcium preparations studied.

Effects on serum parathyroid hormone concentration. One of the normal effects of an increase in serum calcium concentration is a decrease in the concentration of circulating parathyroid hormone (Reginsgter et al., 1993; Heller et al., 1999; Heller et al., 2000; Heaney et al., 2001). Like serum calcium, serum iPTH concentrations are subject to diurnal variation (Nielsen et al., 1991; McKane et al., 1996); this may be the reason that iPTH values for the

placebo group in Figure 2 are seen to fluctuate. In all four groups the observed decreases in circulating iPTH (Figure 2) reflected well the corresponding increases in serum calcium concentrations (Figure 1). Thus, while the changes in iPTH following calcium carbonate administration were not significantly different from placebo, calcium citrate elicited a gradual decrease in circulating iPTH that became significantly greater than placebo (and calcium carbonate) at 180-270 minutes post dose. In contrast to the mild, graded decrease in serum iPTH after calcium citrate, calcium formate caused a much larger decrease in serum iPTH that occurred much more rapidly than after any other treatment and that persisted throughout the observation period. The decreases in serum iPTH concentrations after calcium formate were significantly greater than those after other treatments at all times from 30 to 270 minutes post dose. Overall, however, there was a good correlation between the ability of a given calcium preparation to increase serum calcium concentration and its ability to cause a decrease in circulating iPTH after oral administration. One reason for the apparent flatness of the iPTH vs. time curve for calcium formate in Figure 2 is that with this compound only, the decrease in iPTH was so great that many of the individual measurements were below the lower limit of quantitation. Since this latter value was used in the tabulation, instead of recording a zero or having missing data in the statisitical analyses (see experimental methods), the curve shown may under-represent the true mean decrease in iPTH after calcium formate.

Discussion

For efficient absorption from the gastrointestinal tract calcium must be present in a soluble form, generally as Ca++ ions which are hydrated by solvent water or loosely complexed to anionic ligands in solution. Calcium is absorbed from the gastrointestinal tract by a combination of active transport and passive diffusion (Ireland et al., 1973; Blanchard et al., 1989; Charles, 1992; Guéguen et al., 2000). The active component is saturable, stimulated by 1,25-dihydroxyvitamin D3, and predominates in the duodenum and proximal jejunum; the passive process is more important in the distal jejunum and ileum where transit times are longer, and may become the predominant mechanism for absorbing large loads of calcium which saturate the active process. Many studies of calcium absorption have employed a single oral dose, often 250-500 mg but not infrequently up to 2000 mg of elemental calcium. The fractional absorption of a given oral calcium load varies inversely with the logarithm of the load size in the range 15-500 mg calcium (Heaney et al., 1990), and separate exponential equations have been derived to describe fractional absorption data for men and women subjects as a function of dose size (Heaney et al., 1985). However, at larger loads (i.e. 300-2000 mg) the absolute amount absorbed increases linearly with load size, consistent with a relatively greater role of passive processes over the saturable active process. Calcium absorption has also been modeled by fitting the amount absorbed (as opposed to the fraction of dose absorbed) to an equation with a hyperbolic (i.e., Michaelis-Menten like) term for the saturable process and a linear term for the non-saturable process (Blanchard et al., 1989). Overall, both models describe the data well over a range of calcium intakes up to 2000 mg/day.

Our choice of a 1200 mg dose of calcium was based in part on a desire to compare calcium formate to other common dietary supplements under realistic conditions where both

active and passive absorption mechanisms were likely to contribute significantly. Although it has been shown that multiple small doses of calcium carbonate are somewhat more efficiently absorbed than an equivalent amount given as a single oral dose (Heaney et al., 2000), for reasons of experimental simplicity we chose to administer a single moderately large dose of each form of calcium.

Another factor that can influence calcium absorption is the co-administration of food, the effects of which can be positive or negative (Heaney, 2001; Abrams, 2003). For example, phytic acid and oxalic acid are widely cited as examples of plant constituents which form complexes with calcium and impede its absorption (Weaver et al., 1991; Charles, 1992; Guéguen et al., 2000). On the other hand a simple meal of toasted white bread with cofffee or diet cola has been shown to enhance the net absorption of calcium from calcium carbonate and calcium citrate by 10-30% (Heaney et al., 1989). Calcium supplements are usually taken with meals, and a positive food effect of this magnitude could convey a significant advantage to the individual taking the supplement. In our study, however, we elected to avoid co-administering food in order to obtain a simpler, more direct comparison of the three calcium sources per se. In particular, food would have delayed gastric emptying, thus blunting the onset of intestinal absorption and potentially masking differences between the compounds in terms of their ability to present calcium in an absorbable form to the relevant absorption sites.

Our observations appear to have borne this out. Calcium formate, which is much more soluble than calcium carbonate, and much more dissociated in solution than calcium citrate, was absorbed much more rapidly than either of the latter two sources. The absorption of formate ion from calcium formate in these same subjects was also very rapid, as previously reported (Hanzlik et al., 2005). The more rapid onset and more rapid net rate of absorption of calcium formate led

to a much greater ΔCmax, a much shorter t_{max}, and a much greater ΔAUC for serum calcium increment. These differences between calcium formate and the others are much greater than those that might have been expected for co-administration with food, or for giving multiple small doses instead of a single large dose.

The time course over which calcium absorption takes place is affected by a number of variables including size of dose, rate of gastric emptying, and rate of disintegration and dissolution of the dosage form to release absorbable calcium. In addition, the length of time post-dose over which observations are made and the number of observations made across this time period might also influence the apparent results. Heaney et al. (2001) compared the serum calcium concentration vs. time curves (0-24 hr) after administration of two forms of calcium carbonate, one form of calcium citrate, or a placebo to a group of 24 postmenopausal women. Pharmacokinetic analysis of the data showed no significant differences among the three calcium preparations in terms of ΔC_{max}, t_{max}, ΔAUC (0-5 hr or 0-24 hr), or the bioavailability of calcium, although all three treatments were significantly different from placebo. In this study serum calcium concentrations rose by 5-6% within 3 hr, remained essentially constant from 3-5 hr and then decreased. Heller et al. (1999) also used a pharmacokinetic approach to investigate the relative bioavailability of calcium (500 mg) from calcium carbonate and calcium citrate in 18 healthy women, but found a greater bioavailability of calcium from the citrate than from the carbonate. In a subsequent study Heaney (2003a) administered 300-500 mg doses of precipitated calcium carbonate (enriched with ^{45}Ca) to 12 healthy men. A serum calcium concentration vs. time profile similar to that in his earlier study in women (Heaney et al., 2001) was observed. Significantly, the absorption fraction (determined from the 5-hr specific activity of serum ^{45}Ca) was strongly and linearly correlated to the ΔAUC for serum calcium increment integrated out to

24 hr when the absorption phase would certainly have been completed. Thus, while the length of our observation period was probably not sufficient to capture the entire absorption profile of each calcium compound, it was more than adequate to demonstrate a very significant difference in absorption rate and net calcemic response between calcium formate and the others.

Changes in serum calcium are often mirrored by opposite but amplified changes in serum iPTH concentration; these changes are thus a pharmacodynamic indicator or biomarker of changes in serum calcium. For example, a 5% increase in serum calcium can elicit a 40-50% decrease in serum iPTH (Reginsgter et al., 1993; Heaney, 2001; Heaney, 2003b). Importantly, decreases in serum iPTH sometimes occur after ingestion of a calcium source even when a calcemic response is not clearly evident (Martini et al., 2002; Wood et al., 2003). The serum iPTH changes we observed after placebo, calcium carbonate or calcium citrate were not unlike those reported in other recent studies (Reginsgter et al., 1993; Heller et al., 1999; Heller et al., 2000; Heaney et al., 2001). However, in terms of the rate of onset, magnitude of effect, and duration of maximum effect, the changes observed in these other studies were all considerably smaller than those observed after ingestion of an equivalent amount of calcium as calcium formate.

The benefits of calcium supplements to bone strength and health are thought to derive from both the increased availability of serum calcium for bone deposition and the decreased stimulation of bone resorption by circulating iPTH (Sakhaee et al., 1999; Heller et al., 2000). The fact that calcium formate gave substantially and significantly greater increases in serum calcium concentration, greater ΔAUC for serum calcium increment, and greater decreases in iPTH than equimolar amounts of calcium from supplements based on calcium carbonate or calcium citrate, suggests that calcium formate may have considerable promise for use as a new

dietary calcium supplement. Further studies will be required to evaluate more fully this new source of orally bioavailable calcium.

In conclusion, dietary supplementation with calcium is necessary to good health for some individuals, and is widely practiced by many others. The relative advantages of calcium citrate vs. calcium carbonate as dietary supplements have been extensively studied but continue to be debated, in part because the differences often appear to be small and method-dependent. The present study has shown for the first time that calcium formate was clearly superior to both calcium carbonate and calcium citrate in its ability to deliver calcium to the bloodstream and to depress serum iPTH after oral administration. The high oral bioavailability of calcium formate, combined with its low molecular weight, high percentage of calcium content, and high aqueous solubility at neutral pH, suggest that its potential for use as a dietary calcium supplement merits further investigation.

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Footnotes

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Figure Legends

Figure 1. Changes in serum calcium concentration following administration of a placebo or 1200 mg of calcium as calcium carbonate, calcium citrate or calcium formate, shown as mean ± SEM (n = 14). For these four groups the pre-dose calcium concentrations (mean ± SEM, n = 14) were 10.12 ± 0.13 mg/dL, 9.87 ± 0.11, 9.70 ± 0.12, and 10.12 ± 0.13 respectively.

Figure 2. Changes in serum iPTH concentation following administration of a placebo or 1200 mg of calcium as calcium carbonate, calcium citrate or calcium formate, shown as mean ± SEM (n = 14). For these four groups the pre-dose iPTH concentrations (mean ± SEM, n = 14) were 53.4 ± 4.5, 47.1 ± 5.8, 54.8 ± 6.2, and 46.5 ± 4.7 pg/mL, respectively.

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Table 1. Comparisons of Serum Calcium and Intact Parathyroid Hormone Concentrations Among Treatment Groups. Individual data were converted to percentages of their respective zero-time values prior to analysis.

	Serum Calcium[1]		Serum iPTH[2]	
Comparison	F(1,13)	p	F(1,13)	p
Formate vs. Placebo	28.680	<0.001	31.195	<0.001
Formate vs. Citrate	49.344	<0.001	47.644	<0.001
Formate vs. Carbonate	58.812	<0.001	56.656	<0.001
Citrate vs. Placebo	6.589	0.023	2.664	NS[3]
Citrate vs. Carbonate	15.432	0.002	12.433	0.004
Carbonate vs. Placebo	0.140	NS	0.183	NS

[1] Main-effect pairwise comparisons for serum calcium are based on the data shown in Figure 1.

[2] Main-effect pairwise comparisons for serum iPTH are based on the data shown in Figure 2.

[3] NS means main effect difference is not significant ($p > 0.05$).

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Table 2. Pharmacokinetic values for serum calcium increment after administration of calcium carbonate, calcium citrate, calcium formate or placebo. Values given are the mean and the 95% confidence interval. Values whose confidence intervals do not overlap are significantly different ($p<0.05$).

	Placebo	Carbonate	Citrate	Formate
ΔCmax (mg/dL)	0.81 (0.58 – 1.05)	0.72 (0.56 – 0.89)	1.11 (0.94 – 1.29)	2.14 (1.77 – 2.51)
ΔCmax (%)	8.1 (5.8 – 10.4)	7.4 (5.6 – 9.2)	11.6 (9.5 – 13.6)	21.4 (17.4 – 25.4)
ΔAUC (mg•min/dL)	107 (59 – 154)	91 (58 - 125)	178 (141 – 214)	373 (308 – 437)

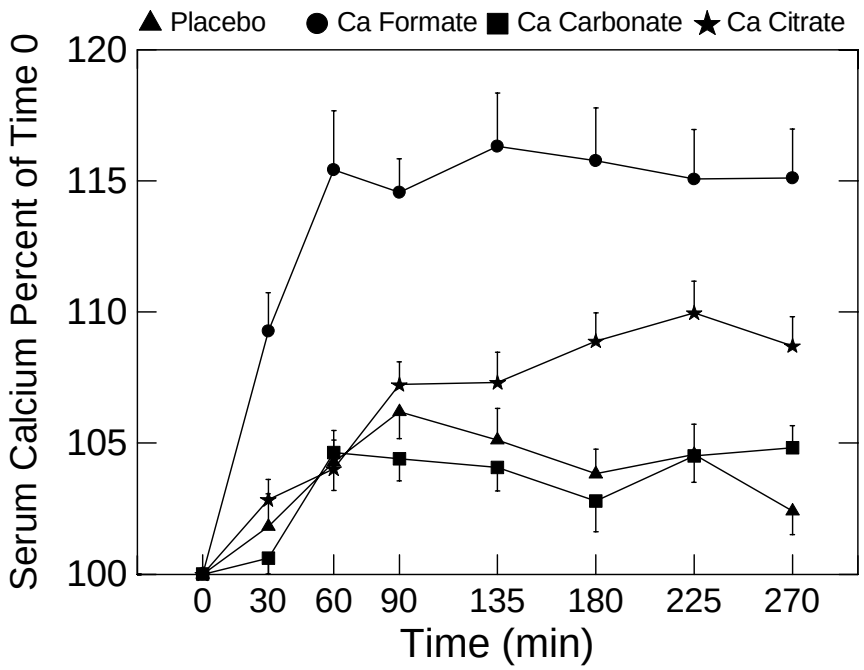

Figure 1

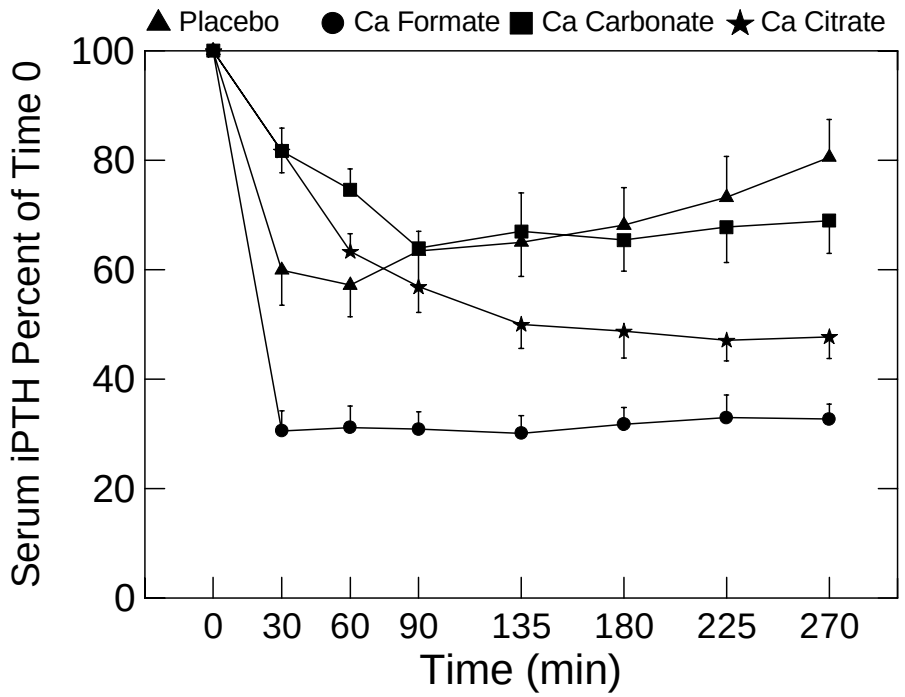

Figure 2