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Panel Session: Nutrition/Exercise

Factors To Consider in the Selection of a Calcium Supplement

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Synopsis

Calcium supplements are widely used, yet many questions remain as to the absorption of various calcium salts. Because the solubility of many calcium salts is dependent upon pH, the type of salt used, the condition of the patient, and the time of administration should be considered. Studies show that many calcium supplements on the market today do not meet standards of quality established in the "U.S. Pharmacopeia" (USP). Consumers must be discerning about the products they purchase. Calcium supplements should be taken with meals to ensure solubility. Calcium carbonate, and particularly tribasic calcium phosphate tablets, are not recommended for patients with achlorhydria. Calcium tablets, like almost all drugs, should be taken with 8 ounces of water or other liquid.

IN SPITE OF the wide use of calcium supplements for the prevention and treatment of osteoporosis, considerable confusion remains about calcium absorption, particularly as to what salt provides optimal bioavailability, and when supplements should be taken. Some of the basic biopharmaceutic and pharmacokinetic principles established for drugs may be applied in considering the administration and absorption of calcium.

For many years, all calcium supplements were thought to be equally effective, as long as an equivalent amount of calcium was ingested. It is increasingly obvious that this is not true. The absorption of calcium is both an active and a passive process. However, regardless of the process involved, calcium must be in solution as ions to be absorbed. Of the various dietary factors that affect absorption, those that have a negative effect (that is, phytates, oxalates, phosphates, and fiber) reduce solubility.

On the other hand, numerous researchers have reported that milk or milk products enhance the absorption of calcium because milk contains a more soluble calcium-protein complex, and milk increases acid secretions and residence time in the stomach; both of these conditions increase the solubility of calcium, and thus promote absorption.

The relative solubility of calcium is complicated by the fact that, for many salts, solubility is dependent on the pH of the dissolution medium. Thus, variations in gastrointestinal pH, which are known to exist, have a direct and substantial influence on dissolution and bioavailability. What does all of this mean when choosing a calcium supplement, and in determining when during the day to take it?

Sources of Calcium for Supplementation

In the past, the choice of a calcium product has often been based on the amount of calcium in a particular chemical compound. Using compounds such

Table 1. Relative calcium content of various salts

Salt	Calcium (percent)	Salt (g) containing 100 percent RDA[1]
Calcium carbonate	4.0	2.5
Tribasic calcium phosphate	38.8	2.6
Calcium sulfate	36.1	2.8
Dibasic calcium phosphate	29.5	3.4
Calcium citrate	24.1	4.15
Calcium lactate	18.4	5.4
Calcium ascorbate	10.3	9.75
Calcium gluconate	9.3	10.75

[1]RDA = Recommended Daily Allowance; for calcium, 800 mg per day.

Table 2. Fate of calcium tablets in gastrointestinal tract

Disintegration	With meals	Empty stomach
Fast =	Dissolves rapidly, slowly passes into duodenum (best absorption)	Slower dissolution (less acid) particles clear rapidly into duodenum
Slow =	Tablet remains in stomach until disintegrated or swept out by "housekeeper" wave	Rapid transit into intestine, no disintegration or dissolution (poor or no absorption)

as calcium carbonate and phosphate allows for the ingestion of larger amounts of calcium while taking fewer tablets. This is an important consideration because the Recommended Daily Allowance for calcium is so high. As shown in Table 1, a person would need to ingest 5.4 grams (g) calcium lactate to obtain the same amount of calcium found in 2.5 g calcium carbonate. Unfortunately, the organic salts that have a high calcium load, such as the phosphate and carbonate, also have a solubility that is pH dependent; thus, they may present the greatest potential for bioavailability problems. The lactate and citrate salts contain less calcium per gram, but their solubility is more independent of pH.

Evaluation of Commercial Products

Because of known drug bioavailability problems that sometimes occur when the less-soluble calcium salts are used as fillers in tablets and capsules, a study was designed to compare the effect of pH on the rate of dissolution of calcium from commercial calcium tablets used as supplements.

An unexpected problem immediately developed, in that many of the commercial products did not meet United States Pharmacopeia (USP) standards for disintegration (*2*) or dissolution (*3*). Eighteen of the 35 products tested did not disintegrate within 30 minutes in 0.1 NHCl, and 11 out of 21 products took longer than 30 minutes for 75 percent of the calcium to dissolve when tested in the same medium. Nationally advertised, and some private-label products, met the standards, while many house brand and/or private-label products did not. Since publication of this work, physicians have reported observing calcium tablets in x-rays, and in patient stools.

Why is it important for calcium tablets to disintegrate and dissolve rapidly? The pH of the gastrointestinal tract varies from a low of 1.0 in the stomach (high acidity) to neutral or slightly basic in the colon. If a calcium tablet does not disintegrate in the stomach, there is little chance that it will disinte-

Table 3. Disintegration and dissolution of commercial calcium carbonate tablets which fail USP standards (October 1987)

Product	Strength (mg)	Lot number	Expiration date	Disintegration time (minutes)	Amount dissolved in 30 minutes (percent)
Food Plus D	250 (OS)[1]	21361	1/91	20	54
Ames Natural Super	500 (OS)	02871501	5/90	> 60	2.8
Ames Calcium-D	600	01872638	5/90	32[2]	2.9
Freeda Drugs Calcium	650	1010	—	22[2]	20
K-Mart Natural-D	250 (OS)	H63522	8/89	57	18
K-Mart Extra Strength	500 (OS)	60319420	3/90	> 60	4.3
K-Mart Calcium	600	70202848	2/89	> 60	4.0
Cambridge Vitamin Calcium	600 (OS)	5723	—	> 60	2.5
GNC Potent Calcium	600	F15952C0	4/92	> 60	42
Revco Calcium-D	250 (OS)	077X1022	7/89	> 60	6.6
Safeway Calcium	325	H65491	1/89	> 60	9.0
Safeway Natural-D	250 (OS)	A71691	1/90	> 60	5.4
Vitaline Corp	250 (OS)	12129	10/89	> 60	6.0
Rite-Aid Hi-Calcium	500	M62841	10/91	51	24
Natural Sales—Sea Calcium (GNC)	500	2G6369FN	6/91	> 60	3.7
GNC Calcium-D	600	1G10965R0	1/90	> 60	2.0
Approved Pharm. Calcium-D	250 (OS)	01713	7/89	> 60	3.0
American Stores	500 (OS)	027200	2/89	> 60	6.2
Your Life	500 (OS)	K62541	9/91	40	56
Long's Drug Calcium-D	250 (OS)	60718903	7/90	2.0[2]	18
Rugby Lab	500 (OS)	10853291	1/89	> 60	1.8
Medicine Shoppe Calcium-D	500 (OS)	022	8/92	> 60	2.2
Medicine Shoppe Calcium-D	250 (OS)	117	7/92	> 60	2.3
Sun Pride Nutrition	500 (OS)	56601	—	> 60	15
Giant Food	250 (OS)	22225	4/91	35	20

Table 4. Disintegration and dissolution of commercial calcium carbonate tablets which meet USP standards—(October 1987)

Product	Strength (mg)	Lot number	Expiration date	Disintegration time (minutes)	Amount dissolved in 30 minutes (percent)
K-Mart High Potency Calcium	600	G60701	7/91	8.0	79
Revco Calcium	600	126452	12/89	2.0	76
Safeway HiCalcium-D	250	H62641	7/89	14.0	102
Rite-Aid Calcium	250 (OS)[1]	B70283	2/90	5.0	77
Hudson Calcium	600	M02132	2/89	10.0	89
Fields of Nature	500 (OS)	087X101	8/89	2.0	90
Giant Natural Calcium-D	600	21493	12/89	4.0	87
Giant Calcium-D	250 (OS)	22090	—	7.0	86

[1] OS = oyster shell

grate or dissolve in the intestine because of the sharp increase in pH which occurs there. This is particularly true when a calcium tablet is taken on an empty stomach, or with a very light meal, when the acidity of even the stomach is low and the contents (including the tablet) are rapidly passed into the duodenum. In this case, there is little or no chance for dissolution to occur. On the other hand, when a tablet is taken with meals, the tablet will generally remain in the stomach for a much longer time, the acidity is greater, and dissolution has a better chance of taking place. These observations are summarized in Table 2.

To update the data on the quality of commercial calcium products, new products were purchased from drug, department, and health food stores during September and October 1987, and submitted to similar test procedures. The results, shown in tables 3–5, illustrate that a serious problem still exists. Over one-half the products tested still did not meet acceptable standards. Based on information from manufacturers of many calcium supplement tablets,

formulations apparently are being changed, but defective products remain in the marketplace.

Why is the quality of calcium products so poor? Calcium tablets are not labeled as drugs, and are sold only as nutritional supplements. Thus, they are not regulated as drugs, and standards characteristic of drug products often do not exist or are not enforced. Because the dose of calcium is so high, companies tend to make tablets very hard, which, while making them small enough to swallow, impedes mechanical digestion, and often omit excipients such as starch that would aid in disintegration. Some manufacturers actually use shellac, which is known to be insoluble in an acidic medium, in their tablet coatings. In any case, some type of regulatory action needs to be taken immediately to ensure that all calcium supplements in the marketplace meet USP standards.

In the meantime, what are consumers to do to ensure that the calcium tablets they are taking are providing maximum benefit? A simple test is to place one tablet in a glass of vinegar at room temperature and stir vigorously for one-half hour. If the tablet has not disintegrated into fine particles by that time, it is probably not properly formulated. Although this is not an absolute test, it correlates in most cases with standard test procedures.

Comparison of Carbonate, Phosphate, and Lactate Salts

Studies were also conducted on the dissolution of calcium from commercial products containing three different calcium salts (calcium carbonate, tribasic calcium phosphate, and calcium lactate) in dissolution media whose pH ranged from 1.01 to 6.09. All of these calcium tablets disintegrated rapidly (less than 6 minutes) but, as expected, dissolution varied dramatically with pH. The data on Os-Cal, Posture, and calcium lactate tablets are shown in table 6.

While the solubility of some calcium salts (mostly those with low calcium loads such as lactate, citrate, and gluconate) is relatively pH-dependent, this is not true for the most widely used calcium supplements—carbonates and phosphates. The solubility of both of these salts is depressed as pH increases. For instance, at pH 4.78, only 10.3 percent tribasic calcium phosphate dissolves in 900 ml 0.1 N HCl after 60 minutes, compared with 77.7 percent for calcium carbonate and 100.8 percent for calcium lactate. Less than 6 milligrams (mg) calcium would be dissolved from a 600 mg tablet of calcium phosphate if it was taken with 3 ounces (oz) (90 ml) water. This is particularly a problem with elderly patients, who have reduced gastric secretions and who tend to drink less fluid than younger patients.

Table 5. Effect of pH on dissolution (percent) of commercial calcium supplements

Buffer	pH	Calcium carbonate[1]		Tricalcium phosphate[2]		Calcium lactate[3]	
		30 min	60 min	30 min	60 min	30 min	60 min
HCl	1.01	87.6	95.7	55.9	80.3	95.5	97.3
Lactate	3.15	82.2	93.9	28.8	49.1	—	—
Acetate	4.78	65.4	77.7	7.2	10.3	92.0	100.8
Citrate	6.09	10.0	22.8	7.3	14.8	96.0	104.6

[1]Os-Cal, 500 mg, Marion Laboratories.
[2]Posture, 600 mg, Ayerst Laboratories.
[3]Five 85-mg tablets per flask, Upjohn.

In a recent study, Recker (*4*) compared the absorption of calcium in its carbonate form to a pH-adjusted citrate form in achlorhydric and normal subjects. There was no difference in fractional calcium absorption from the two forms in normal subjects, but under fasting conditions, the absorption of calcium from the carbonate salt was substantially lower than from the citrate in achlorhydric patients.

Administration of Calcium Supplements

It is generally accepted today that the optimal time to take calcium supplements is with meals. This is certainly true of carbonate and phosphate salts. It is of less significance for citrate or lactate salts. In either case, 6 to 8 ounces of water should be drunk to enhance solubility. Some persons pride themselves on being able to swallow tablets or capsules with only small quantities of water. This should never be encouraged. It may be both dangerous and counterproductive in obtaining maximal benefit from both drugs and nutritional supplements.

The problem of standards for nutritional supplements extends beyond calcium. The Food and Drug Administration (FDA) recently recalled a lot of ferrous sulfate tablets that did not disintegrate. In light of the standard formulation procedures used by some manufacturers of nutritional supplements, many vitamin and mineral supplements may be defective.

Although there is much to be learned about calcium supplements, the principles of bioavailability accepted for drug substances must be applied to their formulation, and only products meeting high standards of quality should be utilized.

Table 6. Disintegration and dissolution of commercial calcium carbonate tablets—(October 1987)—controls

Product	Strength (mg)	Lot number	Expiration date	Disintegration time (minutes)	Amount dissolved in 30 minutes (percent)
Os-Cal	500 (OS)[1]	55548	1/89	7	104
Caltrate-D	600	168-528	12/89	12	77
Tums[2]	200	0766-0740-52	12/91		102
Giant Natural	600	21593	1/90	7	107

[1]OS = oyster shell.
[2]Broken into pieces before testing.

Summary

1. There is a serious problem with the quality of many calcium supplements in the marketplace today, and FDA should immmediately address this issue.
2. Consumers should insist that the calcium supplements that they buy meet USP standards.
3. Calcium supplements (carbonates, phosphates) are best administered at mealtime. They should always be taken with a full glass of water, juice, or other liquid to enhance solubility.
4. The use of calcium salts (in which solubility is pH-dependent), particularly tribasic calcium phosphate, should be avoided in achlorhydric patients.

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Panel Session: Nutrition/Exercise

Is Osteoporosis a Pediatric Disease? Peak Bone Mass Attainment in the Adolescent Female

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Synopsis

Osteoporosis in the elderly woman is determined by the amount of peak bone mass in adolescence, the premenopausal maintenance of such peak bone mass, and the rate of postmenopausal bone mass loss. The majority of research efforts in the past have been directed at defining the pathogenesis and treatment of postmenopausal osteoporotic bone loss. A comparatively new, and potentially fertile, area of research deals with factors responsible for attaining and augmenting peak bone mass in the adolescent female.

Determinants of peak bone mass include genetic, nutritional, weight loading (exercise), and environmental factors. Nutritional factors, especially calcium, are potentially most amenable to therapeutic manipulation. Current data suggest that calcium deficiency exists in the adolescent female; and, although the current data are preliminary and not conclusive, they suggest that increasing calcium intake may be of value in increasing peak bone mass. However, assurance of compliance in the teenage female population in increasing calcium intake is difficult; relating a disease of the elderly, such as