Harms of Glucose-Lowering Therapy Sometimes Outweigh Benefits

Especially in older patients, the burdens of intensive glucose-lowering treatment for type 2 diabetes—particularly with insulin—may exceed the benefits, suggests a study in *JAMA Internal Medicine*.

A Markov stimulation model was used to examine the impact of treatments to reduce hemoglobin A1c (HbA_{1c}) on diabetes complication rates and quality-adjusted life-years (QALYs), based on published data. The results suggested that treatment benefits varied substantially with patient age. Assuming a low treatment burden, treatments to lower $HbA1_c$ by 1 percentage point had a net benefit of 0.77 to 0.91 QALYs for patients receiving diagnoses of type 2 diabetes at age 45, compared with just 0.08 to 0.10 QALYs for those receiving diagnoses at age 75. At a higher treatment burden (3.7 lost days per year), the harms of HbA_{1c}-lowering therapy exceeded the benefits for 75-year-old patients.

Metformin, with relatively small treatment disutility, was beneficial across age groups: net benefit 1.2 QALYs in a 45-year-old patient and 0.148 QALYs in a 75-year-old patient. The absolute reduction in ESRD risk was nearly 10 times greater in a 45-year-old patient than in a 75-year-old patient: 0.065 versus 0.007.

In contrast, starting insulin in response to later increases in HbA_{1c} had a negative impact on QALYs in all age groups. The absolute reduction in ESRD achieved by starting insulin at age 55 was just 0.013.

The trend in type 2 diabetes treatment has been toward intensive glycemic control with lower HbA_{1c} targets. However, the benefits of treatment may take years to accrue, whereas the burdens and adverse effects begin much earlier.

The new study suggests that treatments to improve glycemic control are beneficial particularly for younger patients with type 2 diabetes. However, intensified treatment—especially adding insulin to metformin therapy—may be of little or no net benefit for older patients. "Thus, shared decision making, in which patient preferences are specifically elicited and considered, appears to be the best approach to making most decisions about glycemic management in patients with type 2 diabetes," the researchers write [Vijan S, et al. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. *JAMA Intern Med* June 30, 2014. doi:10.1001/jamainternmed.2014.2894].

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Switching to Phoslyra® (calcium acetate oral solution) may save them the struggle of swallowing over 3,000 phosphate binder (PB) pills a year.*

Phoslyra®
calcium acetate oral solution
667 mg per 5 mL

The Liquid Option

*Based on a mean of 8.4 ± 4.4 PB pills per day[1]

INDICATION:
Phoslyra is a phosphate binder indicated for the reduction of serum phosphorus in patients with end stage renal disease (ESRD). Phoslyra is administered orally with food.

IMPORTANT SAFETY INFORMATION:

- **Phoslyra is contraindicated in patients with hypercalcemia.**
- **Patients should have serum calcium levels closely monitored and their dose of Phoslyra adjusted or terminated to bring levels to normal.** No other calcium supplements should be given concurrently with Phoslyra.
- Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones.
- There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug 1 hour before or 3 hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range.
- The most common (>10%) adverse reactions experienced with Phoslyra are hypercalcemia, nausea, and diarrhea. Of the observed drug-related adverse reactions, diarrhea (5/38, 13.2%) was more common with Phoslyra than with a solid formulation calcium acetate.
- Phoslyra may cause diarrhea with nutritional supplements that contain maltitol.

For additional important safety information, please see the brief Prescribing Information on this page.

Reference: 1. Sussman E, Mullon C, Ginsberg N, et al. Amount of fluid ingested with phosphate binders in hemodialysis-dependent CKD patients. Poster and abstract presented at National Kidney Foundation 2010 Spring Clinical Meeting, April 15-17, 2010, Orlando, Fla.

Manufactured for and distributed by: Fresenius Medical Care NA, Waltham, MA 02451. For more information on Phoslyra, please contact Fresenius Medical Care NA at 800-323-5188.

PN 102352-01 Rev. A 04/2014

Brief Summary: Consult full package insert for complete Prescribing Information.

INDICATIONS AND USAGE: Phoslyra® (calcium acetate oral solution 667 mg per 5 mL) is a phosphate binder indicated to reduce serum phosphorus in patients with end stage renal disease (ESRD). Management of elevated serum phosphorus levels usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis, and inhibition of intestinal phosphate absorption with phosphate binders.

DOSAGE AND ADMINISTRATION: The recommended initial dose of Phoslyra for the adult dialysis patient is 10 mL with each meal. Increase the dose gradually to lower serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Titrate the dose every 2 to 3 weeks until an acceptable serum phosphorus level is reached. Most patients require 15–20 mL with each meal.

CONTRAINDICATIONS: Patients with hypercalcemia.

WARNINGS AND PRECAUTIONS:

Hypercalcemia. Patients with end stage renal disease may develop hypercalcemia when treated with calcium, including calcium acetate (Phoslyra). Avoid the concurrent use of calcium supplements, including calcium-based nonprescription antacids, with Phoslyra. An overdose of Phoslyra may lead to progressive hypercalcemia, which may require emergency measures. Therefore, early in the treatment phase during the dosage adjustment period, monitor serum calcium levels twice weekly. Should hypercalcemia develop, reduce the Phoslyra dosage or discontinue the treatment, depending on the severity of hypercalcemia. More severe hypercalcemia (Ca >12 mg/dL) is associated with confusion, delirium, stupor and coma. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing Phoslyra therapy. Mild hypercalcemia (10.5 to 11.9 mg/dL) may be asymptomatic or manifest as constipation, anorexia, nausea, and vomiting. Mild hypercalcemia is usually controlled by reducing the Phoslyra dose or temporarily discontinuing therapy. Decreasing or discontinuing Vitamin D therapy is recommended as well. Chronic hypercalcemia may lead to vascular calcification and other soft-tissue calcification. Radiographic evaluation of suspected anatomical regions may be helpful in early detection of soft tissue calcification. The long-term effect of Phoslyra on the progression of vascular or soft tissue calcification has not been determined.

Hypercalcemia (>11 mg/dL) was reported in 16% of patients in a 3-month study of a solid dose formulation of calcium acetate; all cases resolved upon lowering the dose or discontinuing treatment. Maintain the serum calcium-phosphorus product (Ca X P) below 55 mg^2/dL^2.

Concomitant Use with Medications. Hypercalcemia may aggravate digitalis toxicity. Phoslyra contains maltitol (1 g per 5 mL) and may induce a laxative effect, especially if taken with other products containing maltitol.

ADVERSE REACTIONS: No clinical trials have been performed with Phoslyra in the intended population. Because the dose and active ingredients of Phoslyra are equivalent to that of the calcium acetate gelcaps or tablets, the scope of the adverse reactions is anticipated to be similar.

Hypercalcemia is discussed elsewhere *[see Warnings and Precautions]*.

Clinical Trial Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical studies, calcium acetate has been generally well tolerated.

The solid dose formulation of calcium acetate was studied in a 3-month, open-label, non-randomized study of 98 enrolled ESRD hemodialysis patients and in a two week double-blind, placebo-controlled, cross-over study with 69 enrolled ESRD hemodialysis patients. Adverse reactions (>2% on treatment) from these trials are presented in Table 1.

Table 1: Adverse Reactions in Patients with End-Stage Renal Disease Undergoing Hemodialysis

	Total adverse reactions reported for calcium acetate n=167	3-mo, open-label study of calcium acetate n=98	Double-blind, placebo-controlled, cross-over study of calcium acetate n=69	
			Calcium acetate	Placebo
Preferred Term	n (%)	n (%)	n (%)	n (%)
Nausea	6 (3.6)	6 (6.1)	0 (0.0)	0 (0.0)
Vomiting	4 (2.4)	4 (4.1)	0 (0.0)	0 (0.0)
Hypercalcemia	21 (12.6)	16 (16.3)	5 (7.2)	0 (0.0)

Calcium acetate oral solution was studied in a randomized, controlled, 3-arm, open label, cross-over, single-dose study comparing calcium acetate oral solution to a solid formulation in healthy volunteers on a controlled diet. Of the observed drug-related adverse reactions, diarrhea (5/38, 13.2%) was more common with the oral solution.

Postmarketing Experience. The following additional adverse reactions have been identified during post-approval of calcium acetate: dizziness, edema, and weakness.

DRUG INTERACTIONS: The drug interaction profile of Phoslyra is characterized by the potential of calcium to bind to drugs with anionic functions (e.g., carboxyl, carbonyl, and hydroxyl groups). Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones via this mechanism.

There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug one hour before or three hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials with all forms of calcium acetate.

Ciprofloxacin. In a study of 15 healthy subjects, a co-administered single dose of 4 calcium acetate tablets (approximately 2.7 g) decreased the bioavailability of ciprofloxacin by approximately 50%.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category C. Phoslyra contains calcium acetate. Animal reproduction studies have not been conducted with Phoslyra, and there are no adequate and well controlled studies of Phoslyra use in pregnant women. Patients with end stage renal disease may develop hypercalcemia with calcium acetate treatment *[see Warnings and Precautions]*. Maintenance of normal serum calcium levels is important for maternal and fetal well being. Hypercalcemia during pregnancy may increase the risk for maternal and neonatal complications such as stillbirth, preterm delivery, and neonatal hypocalcemia and hypoparathyroidism. Phoslyra treatment, as recommended, is not expected to harm a fetus if maternal calcium levels are properly monitored during and following treatment.

Labor and Delivery. The effects of Phoslyra on labor and delivery are unknown.

Nursing Mothers. Phoslyra contains calcium acetate and is excreted in human milk. Human milk feeding by a mother receiving Phoslyra is not expected to harm an infant, provided maternal serum calcium levels are appropriately monitored.

Pediatric Use. Safety and effectiveness of Phoslyra in pediatric patients have not been established.

Geriatric Use. Clinical studies of calcium acetate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE: Administration of Phoslyra in excess of the appropriate daily dosage may result in hypercalcemia *[see Warnings and Precautions]*.

HOW SUPPLIED/STORAGE AND HANDLING: Phoslyra for oral administration is a clear solution containing 667 mg calcium acetate per 5 mL. Phoslyra is supplied in a 473 mL (16 oz) amber-colored, multiple-dose bottle, packaged with a marked dosing cup. Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. The shelf life is 24 months.

PATIENT COUNSELING INFORMATION: Inform patients to take Phoslyra with meals, adhere to their prescribed diets, and avoid the use of calcium supplements including nonprescription antacids. Inform patients about the symptoms of hypercalcemia *[see Warnings and Precautions and Adverse Reactions]*.

Advise patients who are taking an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy to take the drug one hour before or three hours after Phoslyra.

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