

Updated recommendations on the safe and effective use of
oral sodium phosphates solution

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INTRODUCTION

In January 2006 the Scientific Advisory Panel to C.B. Fleet Company, Inc., issued a “white paper” reviewing the literature on renal failure after use of oral sodium phosphates solution (“OSPS”) and made recommendations to clinicians on the safe and effective use of OSPS as a bowel preparation for colonoscopy and other medical procedures (1). Recent recommendations regarding use of bowel preparation have also been made by a joint professional society task force (2). After reviewing new evidence in February 2007, the C.B. Fleet Advisory Panel is issuing these updated recommendations on the safe and effective use of OSPS. The updated recommendations are as follows. Sections 3 and 5 include updates to the 2006 recommendations:

1. **OSPS should be given to the correct patients.** Accepted contraindications to OSPS include clinically significant renal insufficiency, and conditions that place patients at risk for harm from rapid fluid volume and electrolyte shifts, particularly congestive heart failure or liver disease with ascites. The labeling for OSPS lists other indications for which OSPS should not be used or should be used with caution. To clarify the listing of “kidney disease” in the “Do Not Use” category and “Impaired Renal Function” listed in the “Use with Caution” category, the Advisory Panel continues to recommend to clinicians that OSPS not be used in patients with clinically significant impairment of renal function (1).

The Advisory Panel continues to find insufficient data to recommend a specific serum creatinine level above which OSPS should be contraindicated, although impaired renal function will most certainly exacerbate the hyperphosphatemia induced by ingestion of OSPS. It is important for clinicians to recognize that serum creatinine is a poor predictor of kidney function, as glomerular filtration rate is also predicted by age and body weight. Thus, some small elderly persons with normal or near normal serum creatinine levels may have clinically significant impairment of renal function. There are simple formulas that can aid in converting creatinine to glomerular filtration rate (<http://www.nkdep.nih.gov/>). In all clinical trials of OSPS, patients with contraindications have been excluded and the 45mL x 45mL or the 45mL x 30mL doses were not exceeded (1). There have very rarely been serious adverse events associated with OSPS in these clinical trials, which have typically excluded patients with baseline serum creatinine higher than 1.5 to 2.0 mg-dL (1). As recommended in product labeling, baseline and post-procedural electrolytes and renal function should be considered in patients at risk for volume and electrolyte shifts.

The principal associations between OSPS and the majority of reported cases of acute phosphate nephropathy are female gender and hypertension (3-6). It's uncertain whether the female predisposition reflects lower body weight. The Advisory Panel found insufficient evidence to mandate avoidance of OSPS in patients with these possible risk factors.

2. **The maximum recommended dose for bowel preparation for medical procedures is two doses of 45mL each.** Overdoses of OSPS, often prescribed by physicians, have been the most important cause of life threatening reactions associated with OSPS (1). In clinical practice, some patients are not adequately prepared for procedures after two 45mL doses of OSPS or vomit one or both doses of OSPS. Such patients should not receive additional bowel preparation in the form of laxative and/or enemas that contain sodium phosphates, in order to avoid the risk of toxicity associated with phosphate loads. Because OSPS may be packaged in bottles larger than 45mL, OSPS should be prescribed by volume, rather than by “dose” or bottle (see below regarding dosing interval).

3. **One 45mL dose of OSPS, followed by a second dose of 30mL, is an effective alternative to two 45mL doses of OSPS.**

Recent data from two randomized trials indicate that a 15mL reduction in the second dosage (i.e. 45mL first dose and a 30mL second dose) of OSPS demonstrated statistically similar efficacy compared to two 45mL doses and was associated with fewer abdominal side effects and less alteration of serum electrolytes (7,8). Thus, a first dose of 45mL OSPS, followed by a second dose of 30mL, can be used effectively as bowel preparation for colonoscopy (see below regarding dosing interval).

Dose reduction (45mL/30mL) should be considered for patients at risk of dehydration (the elderly) and those that might be at increased risk of phosphate nephropathy (women, those with low body mass index, patients with hypertension). Dose reduction should also be considered for patients on medications known to increase the risk of electrolyte shifts and altered renal perfusion, including angiotension converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory agents (NSAIDS) or diuretics.

- 4. In individuals without contraindications to OSPS, separation of the two OSPS doses by an interval of 6 to 12 hours has been proven to be safe.**

Prescription of OSPS at intervals less than six hours can exacerbate volume depletion and is not recommended by the Advisory Panel or the manufacturer. In clinical trials, administration of one dose the evening before colonoscopy and a second dose on the morning of colonoscopy has resulted in better colon cleansing, compared to two doses given the evening before (1). Splitting the dose between the evening and morning typically also facilitates separation of the doses by an interval approaching 12 hours. The professional labeling for OSPS recommends separation of the doses by 10 to 12 hours. Morning dosing of OSPS must comply with local policies regarding the interval between clear liquid intake and administration of sedation; however, clinicians should be aware that the American

Society for Anesthesiology recommends that clear liquids may be taken up until two hours prior to sedation (9).

- 5. Patients should be instructed regarding the importance of maintaining adequate hydration *before, during, and after* bowel preparation. Specific instructions regarding recommended volume intake should be given in writing to patients. Intravenous hydration should be considered during the procedure.**

Renal insufficiency associated with bowel preparation is in most, and possibly all cases, related to dehydration. *While it's uncertain whether adequate hydration can prevent all cases of phosphate nephropathy, the panel considers that hydration is the most important and promising measure for prevention, considering the likely conditions for and mechanisms by which crystal deposition occurs in the kidney after phosphate ingestion. Therefore, the Advisory Panel believes that the importance of avoiding volume depletion by adequate hydration before, during, and after bowel preparation cannot be overemphasized to clinicians.* Only one report of five cases of Acute Phosphate Nephropathy associated with OSPS discussed the volumes of fluid ingested by the patients doing preparation, and in each case that volume was suboptimal and below the recommended volume (4). Patients typically lose 1 to 1.8 liters of fluid per 45mL dose of OSPS (10). Instructions to patients should emphasize the importance of

maintaining hydration and recommend specific minimum volumes for intake before, during, and after the process.

Specific instructions should include minimum recommended fluid volumes to be taken on the day prior to colonoscopy and during the hours prior to ingestion of the first dose. The goal should be for the patient to have dilute urine and be well hydrated when the first dose is ingested. Hydration should begin well before the first dose of OSPS is taken. The panel suggests that ingestion of at least 36-48 ounces of carbohydrate-electrolyte solution would be optimal in the 6 hours before the first dose.

In general, at least 72 ounces (approximately 2 liters) of liquid, including the mixing volume, should be taken during the preparation with OSPS. One study showed that carbohydrate-electrolyte replacement solution was superior to simple clear liquids for both maintaining hydration and bowel preparation (12). If the patient is unable to comply with hydration instructions before and during the first dose of OSPS, consideration should be given to not ingesting the second dose of OSPS.

Many colonoscopists administer intravenous (IV) fluids to patients during colonoscopy. The administration of IV fluid represents an additional opportunity for patients to be hydrated. Colonoscopists who infuse IV crystalloids during the procedure are encouraged to administer the entire fluid volumes of 500-1000 mL

during the procedure and in recovery to assist patients with the process of maintaining hydration.

After the procedure, some patients sleep for prolonged periods, potentially exacerbating dehydration. Patients should be encouraged to drink specified volumes of fluid in the hours after colonoscopy to avoid dehydration.

6. Additional comments.

OSPS should be used with caution or not at all when a patient's ability to take adequate fluids is impaired or uncertain. OSPS should be used with caution in the elderly and in conditions associated with increased risk of dehydration. Certain medications are associated with renal insufficiency related to volume changes (e.g. diuretics, ACE inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs). Clinicians should be aware of the possibility of additive renal toxicity when OSPS is administered to patients on these medications. Since the clinical significance of any association between these medicines and acute phosphate nephropathy is uncertain, the Advisory Panel makes no recommendation regarding their discontinuation prior to colonoscopy. Clinicians may choose to discontinue them on the day prior to and the day of colonoscopy if they consider discontinuation to be appropriate, safe, and feasible based on their best judgment of the individual patient's health.

There is limited data on administration of OSPS to children 6-18 years of age. Attention should be directed to the possibility that children may have difficulty understanding and cooperating with instructions for hydration. Adequate hydration during the bowel preparation process is expected to prevent renal toxicity in nearly all patients without contraindications.

7. Concluding remarks.

The Advisory Panel recommends that clinicians review their written patient instruction materials regarding bowel preparation and update them as needed to reflect the specific recommendations in this update.

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