March 2014

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Archaic Apothecary Strengths Confused

The Institute for Safe Medication Practices recently received reports from two different health professionals who expressed concern about the way tablet strength is listed on certain phenobarbital and ferrous sulfate labels. The apothecary measure, grains (gr), is used on the products. Even though the US Pharmacopeial Convention (USP) has banned use of the apothecary system, remnants of it continue to appear on container labels for these and several other products. For example, today you can still find aspirin tablets, sodium bicarbonate tablets, nitroglycerin tablets, and calcium gluconate tablets labeled in grains. The labeling on phenobarbital tablets, which lists the strength in both mg and gr, poses a particular hazard. A 1 grain (1 gr) tablet could be misread and transcribed as 1 g (gram)! In June 30, 1999, a case was published in which a surgical resident read a patient's prescription bottle labels and ordered phenobarbital 500 mg IV daily. The pharmacy label expressed the dose using the apothecary measurement 0.5 gr, which the resident thought meant 0.5 g (500 mg) instead of 0.5 grains (30 mg). The patient received phenobarbital 500 mg IV daily for three days. After the patient suffered respiratory difficulties, the dose was withheld and the patient recovered.

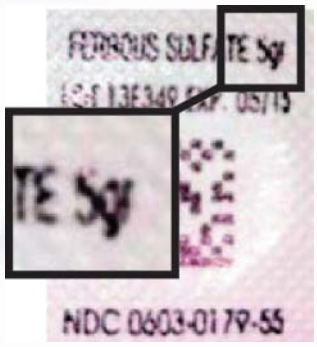

Figure 1.
Will nurses know what 5 gr means?

Use of the apothecary system can also lead to math errors. For example, years ago, when a nurse needed a 1/300 gr (0.2 mg) dose of nitroglycerin for a patient, she administered two 1/150 gr tablets (0.4 mg each) believing 1/150 + 1/150 must equal 1/300. This issue relates in part to "grandfathered" drugs that were around before the Food, Drug, and Cosmetic Act was passed in 1938. Drugs already available then, including those mentioned above, were considered safe enough to remain on the market unregulated by the US Food and Drug Administration (FDA), so the apothecary system is still used in some cases. Since the 1990s, in the General Notices and Requirements section of the US Pharmacopeia/National Formulary, it states that apothecary unit designations on dispensing labels and package labeling shall not be used. Yet it seems like this isn't being enforced. Hopefully, FDA and/or USP will address this situation.

On the other hand…What is the best way to check the label of a high-alert drug when working alone, with no one available to perform an independent check? Use both hands, says Dr. John Senders, Principal Scientific Consultant for ISMP and ISMP Canada. When you pick up a labeled drug vial, the hand almost always obscures some of what's printed on the label. When you use the other hand, that which was obscured often becomes visible and that which was visible becomes obscured. It becomes, in a way, a new and independent check. In addition, according to Dr. Senders, there probably is a right side/left side of the brain effect on the actual reading. The left side of the brain has the machinery associated with speaking and language, so switching hands will take advantage of that. Finally, and most importantly, Dr. Senders believes that people should read the label aloud while holding it in the right hand and perhaps also while holding the container in the left hand.

The Institute for Safe Medication Practices (ISMP) Medication Safety Alert
October 31, 2013

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Mission Statement:
ICP is committed to exceeding our customers' and employees' expectations through quality health-care service, continuous education, and effective communication.

Daliresp continued from page 2

Daliresp experienced severe weight loss which was classified as more than ten percent of original body weight compared to only two percent of patients in the placebo arm.

In conclusion, Daliresp is in a new prescription medication approved for the treatment of bronchitis and COPD. Although it is effective in all patients it seems to have its greatest benefit in patients with more severe forms of COPD. However, since Daliresp is a newer medication without a generic form it is rather expensive for a monthly supply. The most common side effects of Daliresp include: diarrhea, nausea, headache, and weight loss.

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New Extended-Release Namenda Compared to Immediate-Release Formulation

In June 2013, it was announced that the new once-daily extended-release formulation of memantine (Namenda XR) would be available to pharmacies in the United States. The FDA has approved Namenda XR for the treatment moderate to severe dementia caused by Alzheimer's disease. The safety and efficacy of Namenda XR were determined in a randomized trial of 677 outpatients already on a cholinesterase inhibitor by comparing Namenda XR to a placebo in addition to their previous medication. Results from the trial indicated significant benefits in cognition, behavior, and clinical global status in patients treated with Namenda XR compared to those that received the placebo.

Titration and Switching from Immediate-Release to Namenda XR

Patients naive to memantine should be started on 7mg per day of Namenda XR and titrated up weekly in 7mg increments to the target dose of 28mg per day. When switching from Namenda to the XR formulation, it is recommended for a patient on a 10mg twice daily regimen of Namenda tablets should begin taking the 28mg Namenda XR capsules the day after the last 10mg dose of Namenda. In patients with severe renal impairment (CrCl <30), it is recommended to switch from the recommended dose of 5mg twice-daily immediate-release Namenda to 14mg once-daily XR capsules the day after the last 5mg dose of the immediate-release.

Pharmacokinetics

Namenda XR is well absorbed and the maximum concentration is observed approximately 9-12 hours after each dose compared to 3-7 hours for immediate-release Namenda. The overall absorption of both forms of Namenda is not affected by food, but the time it takes to reach maximum absorption is shortened if taken with food. In a study that compared 28mg once daily of Namenda XR with 10mg twice daily of immediate-release Namenda indicated an increased absorption by the XR formulation indicated by Cmax and AUC (24 hr) values 48% and 33% higher with the XR versus the immediate-release.

Conclusion

Compared to target dose of immediate-release Namenda (10mg twice daily), the extended-release formulation of Namenda allows for an increased daily dose and a simplified dosing regimen. This can result in increased compliance and reduced caregiver burden due to the convenience of the once-daily administration of Namenda XR.

There have been no studies comparing the efficacy of the immediate-release Namenda versus the extended release formulation at this time. Until there is adequate research to determine how the efficacy of Namenda XR compares to standard dosing of immediate-release Namenda, it is not possible to determine if one is superior to the other. The XR formulation provides increased convenience for the caregiver and should be considered for any patient with compliance issues or patients that cause a high caregiver burden due to their condition and/or the complexity of their medication regimen.

Jeremy Webster, PharmD Candidate, Ohio Northern University

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Daliresp

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Daliresp (roflumilast) is a phosphodiesterase- 4 inhibitor indicated for the treatment of bronchitis and chronic obstructive pulmonary disease, and is currently the only medication of its kind. It was approved early in 2011 by the FDA and is therefore approximately$207 per monthly supply. Daliresp has shown to provide significant improvement in lung function measured by spirometry and quality of life while significantly reducing the number of COPD symptoms and exacerbations. Daliresp even showed improvement in asthma symptoms. Calverley et al. showed that prebronchodilator FEV1 increased by 48 milliliters with Daliresp compared to placebo. The same study showed that patients with moderate to severe COPD using Daliresp had about 1.14 COPD exacerbations per patient per year compared to 1.37 exacerbations per patient per year for placebo patients. Tsung et al even went as far to suggest Daliresp only provides a net benefit to patients at high risk for exacerbations. Rabe et al. showed similar results as well as significant improvements in health- related quality of life.

The most common side effects that were seen in multiple different studies included headache, diarrhea, nausea, and weight loss. Therefore, Daliresp has labeled warnings for gastrointestinal effects which include weight loss and/or diarrhea and neuropsychiatric effects (depression, anxiety) which are rarely experienced. During the studies, diarrhea was experienced about ten percent of the time and weight loss was experienced from eight to 20% of the time. One study showed that most patients who experienced weight loss typically observed weight loss within six months of starting therapy. In two placebo-controlled clinical trials, 20% of patients treated with Daliresp experienced moderate weight loss classified as five to ten percent of original body weight compared to just seven percent of patients who received placebo. In the same studies, seven percent of patients receiving

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Effectiveness of Calcium Supplements for Treating Hypocalcemia

Many people do not consume anywhere near the recommended amount of calcium in their diets and regularly take calcium (& vitamin D) supplements to maintain normal calcium levels in the body (total calcium: 8.4-10.2 mg/dl; ionized: 3.8-5.3 mg/dl) and to prevent the problems caused by hypocalcemia (i.e. osteoporosis and broken bones). However, recent studies have indicated questionable efficacy of calcium supplements in preventing bone fractures and they have also been found to potentially cause an increased risk of heart attacks and death. This has not been thoroughly studied and requires future research to confirm these claims. However, it may be necessary to use calcium supplementation treatment to avoid the potentially serious symptoms of hypocalcemia.

Symptoms of hypocalcemia are usually observed when calcium levels are ~7-7.5 mg/dl (or <2.8 mg/dl ionized calcium) and can very in severity from asymptomatic to seizures, QT prolongation, and life-threatening tetany, so it is important to address low calcium levels. However, there are many causes of hypocalcemia and supplements may not necessarily be needed to correct the problem. Other imbalances that can cause hypocalcemia should be addressed before supplemental calcium is given. A few common causes are listed below.

1. Vitamin D deficiency: causes decreased calcium absorption
   - Treatment: 50,000 IU 25-hydroxyvitamin D or 0.25-0.5mg 1,25-hydroxyvitamin D
2. Low magnesium: makes it difficult to normalize calcium and potassium levels and should be corrected in every patient
   - Treatment: 2g magnesium sulfate over 10 to 15 minutes, then 1 g/hr
3. High phosphate: usually resolves with intact renal function
   - Treatment: saline + 10-15mg/kg acetazolamide every 3-4 hours
   - Hemodialysis may be needed (especially if impaired renal function)
4. Alkalosis: increases calcium binding to albumin and decreases ionized calcium available; increases severity of symptoms
   - Treatment of metabolic acidosis can have the same effect

Acute symptomatic hypocalcemia (total calcium <7.0 mg/dl or ionized calcium <0.8 mmol) should be treated immediately due to the risk of severe symptoms. The most appropriate treatment (unless there is low magnesium levels) is IV calcium in the form of calcium gluconate. Calcium chloride is not preferred because it causes more tissue necrosis if extravasated.

- IV dosing: 100-200mg of elemental calcium (1-2g calcium gluconate diluted in saline or dextrose) initially over 10-20 min, then a slow infusion at 0.5-1.5 mg/kg/hr
- Continue slow infusion until the patient is receiving effective doses of oral calcium + vitamin D

Chronic hypocalcemia should be treated with oral calcium supplement therapy with a target calcium level of 8.0 because most patients will be asymptomatic and higher levels can cause hypercalciuria. Oral vitamin D supplementation may be needed as well if calcium supplements alone do not achieve the desired calcium level.

- Oral dosing: ~1-2 g/day (elemental calcium) in 2-4 divided doses with food
  - Ex. 500-1000mg $CaCO_3$ (200-400mg elemental calcium) four times a day

When adequate blood levels of calcium are reached with supplementation, it is important to measure urinary calcium excretion and a thiazide diuretic may be added if hypercalciuria is detected to prevent complications including kidney stones and renal impairment. Serum calcium levels should also be monitored closely at first and then every 3-6 months when controlled.

In conclusion, the best way to maintain normal calcium levels in the body and prevent all of the potential complications caused by hypocalcemia (or treatment of hypocalcemia) is to consume the recommended amount of dietary calcium every day from foods/drinks such as milk, yogurt, almonds, kale, broccoli, and calcium-fortified orange juice, etc. However, symptomatic hypocalcemia should not be left untreated due to the potential severity of the symptoms. As far as chronic hypocalcemia, calcium supplementation should be used as recommended until further studies prove that it is not beneficial or that the potential risks of the treatment outweigh the potential benefits.

Jeremy Webster, PharmD Candidate, Ohio Northern University

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