What's New in the Patient Safety World

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Loading Doses Again

It's been over 6 years since we last discussed adverse events related to loading doses of various medications (see our December 14, 2010 Patient Safety Tip of the Week "NPSA (UK): Preventing Fatalities from Medication Loading Doses").

But a recent AHRQ Web M&M brought the issue of problematic loading doses to our attention again (Mucksavage 2017). A patient with a known seizure disorder had a subtherapeutic serum phenytoin level. A neurologist verbally recommended that she be re-loaded with phenytoin. The ED physician ordered the correct loading dose of intravenous (IV) phenytoin, to be administered every 8 hours for 3 doses. But there was miscommunication and the patient was not switched back to a regular maintenance dose after the 3 loading doses. So the patient continued to receive IV phenytoin every 8 hours. And after 3 days developed signs and symptoms of phenytoin intoxication. It was only then that the error was recognized.

Phenytoin, of course, happens to be one of the medications most commonly involved in loading dose errors. In our December 14, 2010 Patient Safety Tip of the Week "NPSA (UK): Preventing Fatalities from Medication Loading Doses") it was one of the 4 medications most commonly involved in such events in the report by the UK National Patient Safety Agency (NPSA 2010), the other 3 being warfarin, amiodarone, and digoxin. In that NPSA report 11% the loading dose was either repeated or continued incorrectly as the maintenance dose as was done in the above case. The NPSA report also noted that handovers and **transitions of care were particularly vulnerable** to missed communications regarding loading/maintenance doses.

Perhaps one of the unspoken issues about the safety of loading doses is asking the question "**Is a loading dose of this medication really needed at this time?**". Over the years we've seen numerous instances where there was probably overaggressive treatment that led to problems. To repeat from our December 14, 2010 Patient Safety Tip of the Week "NPSA (UK): Preventing Fatalities from Medication Loading Doses": for **phenytoin** the answer depends on the clinical circumstances. Obviously for true status epilepticus an intravenous loading dose is appropriately indicated. But for a patient who has had a single seizure (unless that seizure happens to occur during neurosurgery) and is now back to their usual cognitive baseline, an intravenous loading dose is probably not necessary. The gray zone would be in the patient who has had a flurry of several seizures but does not meet the definition of status epilepticus.

The **rate of administratio**n of IV phenytoin (and IV fosphenytoin) is the critical factor in producing hypotension, bradycardia or cardiovascular collapse. The rate is **not to exceed 50 mg/min**. in adults (1-3 mg/kg/minute in neonates) and should be by a **slow IV push**, not an infusion. That means that for a typical loading dose in an adult (1000-1500 mg), the physician would need to spend 20-30 minutes administering the drug. Over the years we've seen corners cut and either the rate would be accelerated or an IV infusion would be used. Some of that is because many neurologists have not seen significant cardiac side effects from IV phenytoin. But those of us old enough to remember giving IV phenytoin to cardiac patients (once upon a time it was used more frequently as a second- or third-line antiarrhythmic agent) recall watching blood pressures bottom out as we increased rates of the IV push. A recent study showed that 39% of patients receiving an IV loading dose of fosphenytoin had hypotension as an adverse effect (Clark 2016). An FDA review (FDA 2010) notes that the majority of cardiovascular deaths (for both IV phenytoin and fosphenytoin) occurred in adults and at recommended doses. Most had pre-existing cardiovascular disease.

Another key issue with phenytoin is use of the wrong dilution technique. It is supposed to be given in normal saline, not glucose solutions. Note also that intravenous phenytoin has been associated with the "purple glove syndrome" (FDA 2010), a rare but serious condition. That was actually the primary reason for the FDA safety review.

The Pennsylvania Patient Safety Authority (PPSA) published one of its advisories on loading doses in 2012 (Carson 2012). They found 580 events related to loading doses over an 8-year period in their Pennsylvania Patient Safety Reporting System (PA-PSRS). Over 70 medications were involved. Vancomycin was the drug most frequently involved, accounting for 14.8% of reports. Ten of the top 20 medications in the PPSA report were also in the top 20 in the UK NPSA study. These were amiodarone, caffeine citrate, clopidogrel, digoxin, gentamycin, heparin, magnesium sulfate, morphine, phenytoin, and vancomycin. Interestingly, warfarin did not make the PPSA top 20 list (warfarin was the most frequently involved drug in the UK NPSA study). Phenytoin was the only drug in the top 5 list in both studies, perhaps not surprisingly given that it is used extensively.

Recognizing that you need to consider loading doses and maintenance doses as part of a package, the PPSA report categorized the events as follows:

- Loading dose omitted or delayed
- Wrong loading dose
- Loading dose given multiple times
- Maintenance dose missed
- Maintenance dose given at wrong time
- Wrong maintenance dose given

Missed or omitted loading dose accounted for 25.5% of their reports. **Patient transfer, either within or between facilities, was a major contributing factor**. For example, the loading dose is often ordered in the ED but the patient transferred prior to receiving it and then only a maintenance dose is given at the destination. Wrong loading doses were often

related to the fact that dose calculations (based, for example, on patient weight) are needed for many of the involved drugs. One specific contributing factor the PPSA noted was that sometimes the pharmacy would deliver a loading dose and maintenance dose to the unit at the same time and staff on the unit would incorrectly select the maintenance dose. Loading dose given multiple times accounted for 7% of reports in both the PPSA and UK NPSA studies. Again, the patient transfer process was a contributing factor in almost 20% of these cases. One factor we'd speculate about would be non-integration of electronic medical records between the ED and the main hospital. In the early days of electronic medical records and CPOE we often saw implementation take place in a piecemeal fashion and ED's often lagged behind or even had different IT systems. So a loading dose given in the ED might not be recorded in the inpatient IT system, creating the opportunity for the double loading dose error.

Fortunately, two of the drugs most often mentioned in the UK NPSA study have likely dropped significantly in rank of medications associated with loading dose errors. First is digoxin. Its dropoff has nothing to do with the risks of loading doses but rather with the significant reduction in the use of digoxin over the last 2 decades.

Second is warfarin. Whereas typical practice years ago was to give a loading dose of warfarin, wait a few days and then resume warfarin at a maintenance dose based upon the INR result, such practice has largely changed. A systematic review in 2010 (Heneghan 2010) concluded that there is no advantage to loading patients with a 10 mg. dose compared to starting with 5 mg. daily and they discouraged use of the 10 mg. dose, particularly in elderly patients. The 10 mg. dose may or may not get the patient to a therapeutic INR faster (depending on which study you read) but may also be associated with early overanticoagulation and there is even some theoretical concern that the loading may actually promote the early hypercoagulability sometimes seen during warfarin initiation. But there are still some who recommend a higher initial dose. More recent recommendations (Witt 2016) are:

- The initial dose of warfarin should be 5 or 10 mg for most patients.
- Beginning on day 3 of therapy, INRs should be measured daily and warfarin doses adjusted to achieve the target INR
- They suggest against using pharmacogenomic testing to determine initial warfarin doses for most patients.

Interestingly, both the CHEST guideline for VTE therapy (Kearon 2016) and the AHA/ACC/HFS guideline for management of atrial fibrillation (January 2014) are silent on loading doses of warfarin. Warfarin loading doses are also becoming less frequent because so many patients are instead being started on novel oral anticoagulants (NOAC's) instead of warfarin. In fact, that new VTE guideline suggests use of non-vitamin K antagonist oral anticoagulants (NOACs) over warfarin for initial and long-term treatment of VTE in patients without cancer (see our February 2016 What's New in the Patient Safety World column "Updated VTE Guidelines from ACCP").

Another drug that has often been associated with loading dose errors is **acetylcysteine**, used for the treatment of acetaminophen poisoning (Hayes 2008). The dosing regimen is

complex, consisting of a loading dose followed by 2 maintenance doses, each with different infusion rates.

As we noted above, **transitions of care** may be particularly **vulnerable** to errors related to loading doses. We've noted that mistakes commonly occur with **ED-to-inpatient** transitions where loading doses are ordered in the ED and the patient is admitted to the hospital. Sometimes the loading dose is assumed to have been given in the ED when, in fact, it was not. Other times the loading dose order is assumed to be the maintenance dose order and very high doses are continued on a daily basis. But another very vulnerable scenario is the **LTC-to-ED-to-LTC** scenario where a long-term care (LTC) patient is seen in the ED but sent back to the LTC facility. Often the notes accompanying the patient back to the LTC are insufficiently clear regarding the recommendations for maintenance therapy and patients may end up getting high daily doses of the medication. Don't rely on just the written notes in such scenarios. A verbal communication with the LTC facility to clarify dosing of that medication can go a long way to avoiding errors.

Lastly, don't forget the most common transition of care: **ED-to-PCP** or **ED-to-SCP**. We remain puzzled in this age of electronic medical records how frequently the physicians responsible for the patient on a daily basis (either the primary care physician or the specialist managing a particular problem) are not made aware that their patient was even in the ED! It's rare enough that the PCP gets notified of the ED visit and sometimes the PCP is notified but the specialist who is the prescriber of the medication at issue does not get notified. Patients after an ED visit are often confused about how to take their medications and may go home thinking they should continue taking the higher dose given in the ED.

The following is a list of the previous NPSA and PPSA recommendations supplemented with some of our own recommendations:

- Review and develop a **list of the drugs** for which loading doses are being utilized **in your organization**. We'll be that phenytoin and vancomycin will likely make your list but, given the disparity between the UK NPSA list and the PPSA list, it is clear each organization must look at its own usage.
- Review any incidents or near-misses related to loading doses that have occurred in your organization and identify contributing factors.
- For those drugs where an immediate loading dose is not necessary, require pharmacist approval of the dose.
- For those drugs where a delay could be deleterious (eg. treatment of status epilepticus or certain arrhythmias), develop a policy requiring two independent verifications of the dose, i.e. the independent double check (keeping in mind the caveats expressed in our October 16, 2012 Patient Safety Tip of the Week "What is the Evidence on Double Checks?").
- Use tools like loading dose worksheets, standardized order sets, clinical protocols, dosing nomograms, or tools to help with dose calculations.
- Ensure proper **communication at all handovers**, both at internal transfers and at discharge, which should include discharge summaries, referral letters, and phone

calls where necessary to ensure **good medication reconciliation at all transitions** of care.

- Ensure that all healthcare workers feel empowered (and obligated) to question any dose of a medication that may appear to be too high. The NPSA alert recommends challenging any initial dose of warfarin greater than 5 mg, amiodarone doses greater than 200 mg daily, digoxin doses greater than 0.25 mg daily (0.125 mg in people over age 70), and phenytoin doses greater than 500 mg daily.
- Always ask the question "**Is a loading dose of this medication actually necessary?**"
- Ensure that your CPOE or e-prescribing systems clearly specify what are orders for loading doses and prevent continuation of those doses beyond the loading period.
- Ensure that for drugs with a loading dose you have programmed **dose range limits** into your CPOE or e-prescribing systems that will alert you of the high dose and query you whether this is a loading dose.
- Explore having your pharmacy deliver loading doses and maintenance doses separately.
- Consider differentiating packaging/labeling of loading doses and maintenance doses.
- For patients not admitted, make sure that you have a means of **communicating details of the ED visit and recommendations for maintenance dosing back to the party overseeing use of that medication on a daily basis** (whether PCP, specialist, or LTC facility).

Technological solutions are obvious potential means to avoid such errors. But does **CPOE** actually reduce the chance of errors with loading doses or could it paradoxically increase that risk? We've seen some pretty "clunky" IT systems that are not particularly user-friendly when it comes to ordering medications. That is **especially so when the order is a complex one** in which different doses of a drug are being given on different days, as is the case with loading doses followed by maintenance doses. Considerable confusion may occur when entering such orders, whether directly entered by the physician or entered by a nurse or pharmacist. We have seen instances where the loading dose of a drug gets continued every day or ones where the patient gets both the loading dose and maintenance dose on the same days. Theoretically, use of **standardized order sets** or protocols (whether paper or electronic) may help avoid such errors but such have not specifically been studied for drugs with loading doses.

The other problem, of course, is that **clinical decision support tools** that can make CPOE and pharmacy computer systems safer are still suboptimally used. Many current systems do not provide **dose range alerts** that would flag a relatively high dose of a medication for verification. Also, most current systems do not require an **indication field** be filled out for each drug. A good system would require input of the indication, with a check box or drop down list where "loading dose" could be indicated (and the system programmed to not continue loading doses beyond the specified time period).

Loading doses can even be a problem when they are not loading doses! One of the medication error slides we like to show is a hand-written prescription for 300 mg of an anticonvulsant that was intended to be taken at bedtime. However, the "S" in "qHS" was missing. The pharmacist interpreted the "qH" as "q4" and assumed that "q4h" was intended. While the pharmacist recognized this would be a very large dose of this anticonvulsant, he also assumed that this was likely a loading dose. It was thus dispensed with the directions to "take every 4 hours" and the patient presented to the ER several days later with anticonvulsant toxicity. We like this particular example because it demonstrates several cognitive biases:

- We see what we expect to see or we fill in the gaps (closely related to "inattentional blindness")
- We often ignore disconfirming information and seek confirming information (pharmacist thought "this must be a loading dose" but ignored the fact the "dispense: #30" did not fit with a loading dose)

Loading doses are an error-prone facet of the medication process, particularly at transitions of care, that have been underrecognized but have the potential to cause significant patient harm. You should consider adding an initiative on loading doses to your medication safety program. At a minimum you should try to get a handle on how often and for which drugs loading doses are being used in your organization.

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