Patient Safety Tip of the Week

June 11, 2013

Amphotericin Mixups Continue

The California Department of Public Health has just issued its latest round of hospital fines for medical errors. We always review these because the root cause analyses and plans of correction included with them usually describe events that could occur at your hospital as well. So they usually have many lessons learned. This round had the typical series of retained foreign bodies, medication errors, and falls with injury. The case that caught our eye, however, was one in which a mixup of amphotericin B formulations led to the death of a pediatric patient (CDPH 2011). This is not a new problem. It has been encountered on multiple occasions and receives attention about every 5 years. There have been excellent reviews and recommendations about this from both ISMP (ISMP 1998, ISMP 2007) and ISMP Canada (ISMP Canada 2002, Koczmara 2011).

While most such incidents have occurred in acute care hospitals, they have also been reported in the home care setting (ISMP 1998).

The problem entails **confusion between conventional amphotericin B and the liposomal formulation of amphotericin B, which have different dose ranges**. In the California case a physician intended to order the liposomal formulation of amphotericin B (Ambisome) to treat a fungal infection in a pediatric patient with acute myeloblastic leukemia and a bone marrow transplant. The actual order, however, was for "amphotericin B, conventional" 375 mg IV every 24 hours. The maximum limit for a single daily dose of conventional amphotericin B is 1.5 mg per kg. For this particular patient, based on weight, the ordered dose was more than three times the maximum limit.

The inappropriately high dose was not picked up during review by a pharmacist nor by the nurse who administered the dose. The patient received the erroneous dose at 10:15 AM and subsequently experienced a cardiac arrest and died at 1:15 PM.

As is usual in cases with adverse patient outcomes, a cascade of errors and enabling factors combined to lead to the adverse outcome:

- The physicians at the facility often used the terms "Ambisome" and "amphotericin B" interchangeably. But they are two different formulations and have different dosage ranges. The usual dosage range for "Ambisome" (the

liposomal formulation of amphotericin B) is 3 to 5 mg per kg, whereas the maximum dose limit for the conventional amphotericin B is 1.5 mg per kg daily.

- Conventional amphotericin B was the first item to be seen on the order entry screen.
- An alert on the order entry screen triggered by ordering conventional amphotericin B prompted the ordering physician to "verify that the dose does not exceed 1.5 mg/kg" but allowed continuation of the order without any other confirmation that the dose did not exceed that maximum.
- When the pharmacist reviewing the order reviewed the patient chart, he noticed that the infectious disease consultant had approved use of "Ambisome", which has a normal dose range of 3 to 5 mg per kg.
- The pharmacist did not note the disparity between consultant's mention of "Ambisome" and the actual order being processed for "Fungizone" (conventional amphotericin B).
- No independent double check was performed prior to administration.

The plan of correction in the California case focused fairly heavily on education. While it is extremely important to bring this issue to the attention of all your clinical staff (that's why were are doing this column!) we also need to be practical. For relatively rare events like this it is very likely that the education will no longer be remembered the next time the opportunity for the error arises. Therefore, it is imperative that we put **system interventions** in place to reduce the chance such events will occur (see our March 27, 2012 Patient Safety Tip of the Week "Action Plan Strength in RCA's" and click here to see some slides we put together to help remember them. Remember: images are more likely to be remembered than words!)

On the CPOE screen for choosing drugs the conventional formulation of amphotericin B appeared as the **first choice in a list**. One problem we've encountered in some CPOE systems is that there are circumstances when multiple preparations of a drug may not appear on the screen at the same time. You may have to scroll down further even in an alphabetical list to see all preparations of a drug. It could be possible for a provider to just see the conventional preparation and not scroll down to see that there was also a liposomal preparation.

One of the interventions put in place in the California case was to eliminate the ability to order conventional amphotericin B for intravenous use from the CPOE system.

Today's CPOE systems have, or should have, the capability to go much further in preventing overdosing with many drugs. Most require that a patient's weight be input into the system. So rather than just having an alert pop up asking the provider to verify that the dose does not exceed 1.5 mg/kg (an alert that can be dismissed with the click of a mouse) the computer should be capable of doing the calculation, determining that the dose does exceed the maximum limit and forcing the provider to contact the pharmacist before that dose is authorized. That sort of **"hard" alert** should be used in cases where the action could be potentially fatal or lead to other very serious consequences.

The approach by the hospital in the California case was eliminating the ability to order conventional amphotericin B for intravenous use from the CPOE system. We are not told whether conventional amphotericin B was removed from the hospital formulary. We suspect it was not removed because there may still be indications for use of the conventional rather than the liposomal preparation. So essentially the California hospital accomplished what we were recommending above as a "hard" alert by instituting a **constraint** or a **forcing function**, i.e. the provider would have to call the pharmacy if he/she actually wanted the conventional amphotericin B preparation. We don't know at this time which of these two approaches might be best. Both might have unintended consequences, such as the provider using the liposomal formulation when the conventional formulation was really indicated.

One recommendation for CPOE from both ISMP and ISMP Canada is to **include the complete generic and brand names** on the computer entry screens.

That same recommendation applies if you are writing an order for the drug. You should include both the complete generic and brand name for the drug. And use of both the generic and brand names should appear on **the MAR** (Medication Administration Record) and other places, such as **ADC's** (automated dispensing cabinets) if these drugs are allowed in ADC's (note below that both ISMP and ISMP Canada strongly discourage storage of amphotericin B products in ADC's).

Use of **standardized order sets** is also very helpful, not just for frequently used regimens but also for less commonly used but high alert medications (like desmopresin or argatroban mentioned below). For amphotericin B your standardized order set can be constructed in a way to clearly differentiate the two drug formulations and help the provider in determining which formulation is used for which indication. On the standardized order set you might also be able to include orders for any ancillary studies you might want in monitoring treatment (eg. you might want to assess renal and hepatic function in a patient on amphotericin B) or interventions to minimize risk of side effects (eg. hydration recommendations). Such standardized order sets can be either paper-based or computer-based.

One recommendation for written orders or standardized order sets is to both **write out the formula** and the total dose for weight-based dosing (ISMP's guidelines for standard order sets). That, of course, helps the pharmacist or the dispensing nurse to perform a double check by redoing the calculation to verify that the total dose is correct.

Speaking of the double check, both ISMP and ISMP Canada recommend **independent double checks** for dispensing and administering amphotericin B. We've often written about the pros and cons of the double check (see our October 16, 2012 Patient Safety Tip of the Week "What is the Evidence on Double Checks?") but we do recommend a true independent double check for high alert medications and would include amphotericin B formulations in that recommendation.

There are some particularly important lessons learned in the 2011 paper written by staff from ISMP Canada (Koczmara 2011). They reported on incidents reported to ISMP Canada involving amphotericin B and noted that 4 of the 5 incidents involved giving conventional amphotericin B when liposomal amphotericin B was intended, thus resulting in doses that were too high.

They really emphasize the **storage** issue. In one case described, conventional amphotericin B was obtained from an automated dispensing cabinet (ADC) by a nurse after an order to "continue amphotericin B" in a patient who had been receiving liposomal amphotericin B. As a result, the authors **discourage storage of amphotericin B products in patient care areas or automated dispensing cabinets (ADC's).** They recommend that all amphotericin B products be restricted to preparing, labeling and dispensing by the pharmacy where there are built-in checking processes. However, they recognize that in circumstances where there might not be night availability of a pharmacist it may be necessary to have some product available elsewhere. In such cases the recommend the following:

- Establish a **maximum quantity** to be available (for example, one hospital allows only a single vial of conventional amphotericin B in the ADC of an ICU).
- Include the **complete generic name and brand name** on the selection screen.
- Include a **warning about the error potential** between preparations.
- Require an **independent double check for the override** function of the ADC.
- A **pharmacist should review all overrides** as soon as possible.

Storage in the pharmacy needs to ensure that the different products are well differentiated (by labels, warnings, etc.).

Both ISMP and ISMP Canada have also noted the **difference in appearance of the IV solutions for the two products**. The conventional product has a clear amber appearance, whereas the liposomal product has a milky amber appearance. So pay particular attention if staff, patients or families note a change in appearance of the solution from one dose to another.

The ISMP Canada papers (ISMP Canada 2002, Koczmara 2011) also highlight another important, but often violated, practice: **when renewing orders always write out the full order**. They cite a case in which a patient was receiving liposomal amphotericin B and an order was given to "continue amphotericin B". A copy of the order was not sent to the pharmacy and for 2 days nurses retrieved conventional amphotericin B from the ADC and administered it before the error was identified.

ISMP Canada also notes you should **always question the need to add more than 2 vials to any IV solution** (ISMP Canada 2002). Adding more than 2 vials should always be considered a "warning flag" and prompt staff to perform extra checks to verify the order. You would be surprised how often we encounter incidents of medication overdoses where we say "didn't they get suspicious when they needed so many vials?" (see our December 14, 2010 Patient Safety Tip of the Week "NPSA (UK): Preventing Fatalities from Medication Loading Doses" for a case where 32 vials of phenytoin were

erroneously used to make up an IV loading dose that was 10-fold higher than the intended dose).

Regarding the educational piece, it is also recommended that **warnings that the two products are NOT interchangeable and have different dosage ranges** be included at every opportunity (inservices, CPOE screens, standardized order sets, pharmacy storage and preparation areas, labels, ADC machines, MAR's, etc.). It's also important to ensure that detailed, technical drug information is easily and readily accessible in those clinical areas that use amphotericin products.

Including a **clinical pharmacist as part of your multidisciplinary rounding team** is a huge advantage for those hospitals that can afford it (we often argue that hospitals cannot afford not to include them). For those that cannot put a pharmacist with each and every physician or service, periodic review of orders with a pharmacist may be valuable. The California hospital began having weekly meetings of a pharmacist with pediatric residents to review errors in orders written and all housestaff now participate in a medication error awareness workshop three times a year.

Don't forget to educate the patient and family (or other caregivers) as well. Since the duration of amphotericin B treatment often exceeds the period of acute hospitalization, patients may have continuation of treatment at home or in alternative settings.

The FDA also has a very good patient safety video "Avoiding Mixups between Amphotericin B Formulations", done in conjunction with ISMP.

Most hospitals' **high alert medication lists** focus on insulin, opiates, anticoagulants, chemotherapy agents, neuromuscular blocking agents and others that might be used frequently at their facilities. However, we often recommend that you include on your list of high alert medications those that are seldom used but, often for that very reason, may be used inappropriately. We've previously talked about argatroban and desmopressin (see our March 18, 2008 Patient Safety Tip of the Week "Is Desmopressin on Your List of Hi Alert Medications?"). Methotrexate might be another (see our July 2010 What's New in the Patient Safety World column "Methotrexate Overdose Due to Prescribing Error" and our May 7, 2013 Patient Safety Tip of the Week "Drug Errors in the Home"). Those drugs that are used infrequently but have a narrow therapeutic index or possible severe adverse side effects are good ones to put on your high alert medication list. These are the ones where development of standardized order sets and hard-stop CPOE alerts may be indicated. **Amphotericin B is another obvious inclusion for your high alert medication list**.

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