ALERT: Mix-ups between conventional and lipid formulations of amphotericin B can be extremely dangerous

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Abstract

In this column, the authors review Amphotericin B incidents reported to ISMP Canada. In particular, we focus on incidents reported to have resulted in patient harm due to mix-ups between the conventional (non-lipid) formulation and lipid formulations of amphotericin B. Although amphotericin B may be less commonly used today because of alternative antifungal agents available, incident reports suggest there continues to be a need to alert practitioners to the different formulations, and to implement system safety strategies.

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An *ISMP Canada Safety Bulletin* was published in 2002 about two incidents where patients received conventional (non-lipid) amphotericin B desoxycholate (Fungizone®) IV, instead of the intended lipid formulation amphotericin B product (Abelcet® and AmBisome®). The safety bulletin highlighted information about such mix-ups, and included information about deaths that had been reported in the United States (ISMP Canada, 2002). Since then, there have been other similar errors reported internationally (Groeneveld, Verweij, Hek, Bökkerink, & Warris, 2008; Mohr, Hall, Ericsson & Ostrosky-Zeichner, 2005) including two fatal cases in the United Kingdom, where non-lipid amphotericin B was ordered and administered, but at doses calculated using lipid-based amphotericin B dosing guidelines (NPSA, 2007). An overview of the learning from a review of the ISMP Canada incident database involving amphotericin errors is shared here. Learning from an incident report recently received from the critical care setting is also shared, along with system improvement opportunities.

Intravenous amphotericin is currently marketed in Canada as conventional (non-lipid) amphotericin B (Fungizone®) and as lipid formulations (AmBisome®—a liposomal formulation, and Abelcet®—a lipid complex formulation). ISMP Canada has received a total of 41 voluntary reports of incidents involving intravenous (IV) formulations of amphotericin B over a period of almost 10 years (January 2001 to November 2010 inclusive); reports include those received from the intensive care unit (ICU) setting. Of the 41 incident reports received, 22% (n=9) were reported to have resulted in patient harm. The majority of these harmful incidents (n=5) involved mix-ups between conventional (non-lipid) amphotericin B and lipid formulations of amphotericin B. (The other four incidents reported with an outcome of harm were: two incidents in which the amphotericin B doses were administered too quickly IV, one incident in which the amphotericin B was administered at the wrong frequency, and one incident in which the first dose was inadvertently omitted in a patient diagnosed with cryptococcal meningitis.) In four of the five incidents involving mix-ups between the conventional and lipid formulations, conventional (non-lipid) amphotericin B was administered when the lipid formulation was intended; (the remaining incident lacked the detail needed to determine the mix-up type). Although it is impossible to infer or project the probability of specific incidents on the basis of the voluntary reports received by ISMP Canada, the information available can be used to identify issues that may require additional investigation or attention.

Information from an incident recently reported is shared:

> *An ICU patient weighing approximately 60 kg was receiving 300 mg IV daily of lipid complex amphotericin B (Abelcet®). After seven days of therapy, a specialist reviewed the patient's treatment and suggested that the amphotericin B be continued (i.e., 'continue amphotericin B'). After approval by the most responsible physician, a copy of the order was inadvertently not sent to pharmacy. For the next two days, nurses caring for the patient retrieved a supply of the conventional (non-lipid) formulation of amphotericin B (Fungizone®) from an automated dispensing cabinet (ADC) and administered 300 mg IV daily. During administration of the Fungizone®, the patient suffered episodes of hypotension requiring treatment. On the third day, the error was identified when the ADCs in the ICU required replenishment of amphotericin B (Fungizone®). The amphotericin B was put on hold and the patient's renal function was monitored closely. The patient experienced acute renal failure, which, fortunately, resolved over time.*

The guidelines for conventional (non-lipid) amphotericin B note that the dose **should never exceed 1.5 mg/kg/day** (Bristol-Myers Squibb Canada, 2009). Doses of the lipid formulations of amphotericin B are higher, but vary among products and indication. For example, the usual dose for the lipid complex Abelcet® is 5 mg/kg/day (Sigma-Tau Pharmaceuticals, 2010) and the usual dose for liposomal AmBisome® is 3 to 6 mg/kg/

day (Astellas Pharma Canada, 2009). [Refer to the drug-specific drug product monographs for more information (Astellas Pharma Canada, 2009; Bristol-Myers Squibb Canada, 2009; Sigma-Tau Pharmaceuticals, 2010).] The inadvertent administration of conventional non-lipid amphotericin B at the higher dose intended for a lipid-based formulation can lead to permanent renal damage and also to potentially fatal cardiac or cardio-respiratory arrest (Bristol-Myers Squibb Canada, 2009).

> Amphotericin B (Fungizone®)—conventional (non-lipid) formulation:
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> *"Under no circumstances should a total daily dose of 1.5 mg/kg be exceeded. Amphotericin B overdoses can result in potentially fatal cardiac or cardio-respiratory arrest." (Bristol-Myers Squibb Canada, 2009, p. 7).*

A number of potential contributing factors to the incident highlighted above were identified by the facility, including:

- Similar names of the two products: amphotericin B and lipid complex amphotericin B.
- The suggested order to continue therapy with lipid complex amphotericin B was incomplete.
- A copy of the new order was inadvertently *not* sent to the pharmacy.
- Six vials, each containing 50 mg of conventional non-lipid amphotericin B (Fungizone®), were available in each of the two ADCs in the ICU.

In an effort to prevent a similar mix-up from recurring, the pharmacy now places only one vial of non-lipid amphotericin B (Fungizone®) in each ADC in the ICU—a maximum of 100 mg or two vials in total. A warning also appears that requires confirmation that the non-lipid amphotericin B is the correct medication.

The following are suggested strategies that can be used by nurses, as well as physicians and pharmacists in an effort to prevent mix-ups between the conventional (non-lipid) and lipid-based formulations of amphotericin B:

- When writing orders or communicating order information, use additional identifiers and both the **complete generic name** and the **brand name:** amphotericin B (Fungizone®) **or** liposomal amphotericin B (AmBisome®) **or** lipid complex amphotericin B (Abelcet®). For Fungizone®, ideally additional descriptors such as "conventional" or "regular" should also be added to the generic name (ISMP, 2007; ISMP Canada, 2002).
- When re-ordering, rewrite the full order, including the **brand name** and **dose**. "Continue amphotericin B" should be considered an incomplete order (ISMP Canada, 2002).
- Ensure that the Medication Administration Record (MAR) includes both the complete generic name and the brand name (Cohen, 2007; ISMP, 2007; ISMP Canada, 2002).
- Ensure that both the generic name and brand name appear in computerized order entry systems for prescribers and in pharmacy. Computer systems, when optimized, can provide critical medication system safeguards, including prevention of an excessive dose (ISMP Canada, 2002). (It may be of interest to note that a commentary submitted by an ICU pharmacist and published in the *British Medical Journal* highlights a reduction in the number of amphotericin formulation mix-ups from several per year to none after several changes were implemented; one of these changes was the inclusion of the brand name in the computerized prescriber order entry system [Badman, 2007].)
- Add warning statements (or warning screens) describing the risk for error, and add maximum dose "flags" to computerized medication order entry systems (ISMP, 1998; ISMP, 2007; ISMP Canada, 2002).
- Amphotericin B products are best restricted to preparation, labelling, and dispensing by pharmacy, where there are built-in checking processes (ISMP Canada, 2002). All labels used in dispensing should include both the generic and brand name (ISMP Canada, 2002).
- The storage of amphotericin B products in patient care areas and automated dispensing cabinets (ADCs) is discouraged (ISMP, 2007; ISMP Canada, 2002). However, it is recognized that an antifungal agent such as amphotericin B may need to be made available to areas such as critical care for urgent after-hours situations and where an on-call pharmacist is not readily available. Related risks with storage, however, must be minimized and may include:
  - Establishing a maximum quantity to be available.
  - Inclusion of the complete generic name and brand name on selection screen.
  - Ensuring a warning appears on the ADC about the error potential between amphotericin B and amphotericin B lipid formulations.
  - Establishing a requirement for an independent double-check for use of the override function for automated dispensing cabinets (e.g., if order cannot be double-checked by a pharmacist and, thus, cannot be profiled for the patient) (ISMP Canada, 2007).
  - Ensuring that overrides occurring with medications such as amphotericin B are reviewed by a pharmacist as soon as possible (ISMP Canada, 2007).

  Similar considerations are also applicable to storage and access of amphotericin B from an "after-hours supply" or a "night cupboard".
- The storage of different amphotericin products in pharmacies needs to be well differentiated. Consider the use of cautionary labels or another mechanism (e.g., warning sign) to remind staff about the differences between the products (ISMP, 2007; ISMP Canada, 2002).
- Add a prominent warning statement to any intravenous manuals, drug charts, or other documents produced by the hospital, specifically describing the potential for error-induced injury with amphotericin B products. (ISMP Canada, 2002; ISMP, 2007). One example of such a warning is the boxed warning found in the product monograph for conventional amphotericin B (Fungizone®) (Bristol-Myers Squibb Canada, 2009).
- Ensure that drug information is easily and readily accessible for all practitioners (ISMP, 2007; ISMP Canada, 2002). Consider preparing an information document to be placed in the patient's chart when amphotericin B is dispensed.
- Verify and double-check the dose prior to prescribing/dispensing/administering amphotericin B, especially if you are unfamiliar with the drug or its dosing (Cohen, 2007; ISMP, 2007; ISMP Canada, 2002).

- If staff, patients or family members notice a change in the solution's appearance, stop and verify that the correct drug is being used. Lipid-based products may be seen as having a "milky" amber colour, rather than the clear amber-coloured solution of the conventional product. In one of the cases described by ISMP (U.S.), the patient's spouse raised concerns on noticing that the colour of the IV solution (Fungizone®) was darker than what had previously been administered, that is, the lipid-based solution (Cohen, 2007; ISMP, 1998; ISMP Canada, 2002).
- Share this information widely in an effort to raise awareness about the availability of different formulations of amphotericin B and that these products require different dosing and are *NOT* interchangeable. It is especially important that any staff required to handle amphotericin be familiar with the various formulations that are available (Cohen, 2007).

It is hoped that this article raises awareness among critical care practitioners about the potential for serious patient harm if a mix-up occurs between conventional and lipid formulations of amphotericin B, and the need for system safeguards.

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ISMP Canada gratefully acknowledges the valuable lessons learned and information reported by professionals in the Canadian health care community that can then be shared to enhance medication system safety. All ISMP Canada Safety bulletins are available from **http://www.ismp-canada.org/ISMPCSafetyBulletins.htm**

ISMP Canada is an independent national not-for-profit organization committed to the advancement of medication safety in all health care settings. ISMP Canada maintains a national voluntary medication incident and 'near miss' reporting program founded for the purpose of sharing the learning experiences from medication errors. Our collaborative goal is implementation of preventive strategies and system safeguards to decrease the risk for error-induced injury.

ISMP Canada is a key partner in the Canadian Medication Incident Reporting and Prevention System (CMIRPS). Medication Incidents (including near misses) can be reported to ISMP Canada: (i) through the website http://www.ismp-canada.org/err_report.htm or (ii) by phone: 416-733-3131 or toll free: 1-866-544-7672.

ISMP Canada guarantees confidentiality and security of information received, and respects the wishes of the reporter as to the level of detail to be included in publications.

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