EDITORIAL

Is BCG a Hazardous Drug? Ask NIOSH, OSHA, and the USP

Answering this question is not easy. However, having universal agreement has become important as regulations on the administration of intravesical BCG in the Urology office are becoming more stringent.

First, we need to clarify the alphabet soup in the title and understand the major organizations who are weighing in on this issue. You most likely know that BCG stands for Bacillus Calmette-Guérin, the live attenuated *Myobacterium bovis* used for decades worldwide to percutaneously immunize against tuberculosis and placed into the bladder as an immunotherapy to treat superficial bladder cancer. As an attenuated organism, *Mycobacterium bovis* is considered non-pathogenic in humans and when properly administered, rarely causes serious side effects in the patient.

NIOSH is the National Institute for Occupational Safety and Health under the umbrella of the CDC (Centers for Disease Control and Prevention). NIOSH is a US Federal agency that conducts research and makes recommendations to prevent work-related injury and illness. Another federal agency, Occupational Safety and Health Administration (OSHA), establishes and enforces protective workplace safety and health standards and requires compliance with NIOSH recommendations.

USP is the United States Pharmacopeia, an independent nonprofit pharmacy centric organization. Their main job is to generate compendia of drug information referred to as a *pharmacopeia*. They also provide guidance on activities related to drug handling and administration primarily for pharmacy professionals. While USP has no regulatory authority, organizations who have that authority (i.e., levy fines or suspension of operations) often require strict adherence to USP guidelines. USP guidelines are published in what is called "Chapters". In terms of the hazardous designation for BCG, USP Chapters 797 and 800 are most important.

Another organization to consider is the FDA (Food and Drug Administration). The FDA approves and regulates medications ln the US. Their pregnancy classifications identify medications based their potential for fetal harm, but they have no specific "hazard" designation.

USP follows the NIOSH hazardous drug listings. NIOSH considers a drug to be hazardous if it exhibits one or more of the following characteristics in humans or animals: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity, organ toxicity at low doses, genotoxicity, or structure and toxicity profiles of new drugs that mimic existing hazardous drugs.[1] How did this hazardous drug classification system come about?

In the 1970's chemotherapeutic agents were associated with secondary cancers and OSHA recommended the use of biological safety cabinets (aka "hoods") for the preparation of these hazardous drugs. This led to a sentinel 2004 NIOSH warning titled "Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings".[2]

With this background we can begin to unfold the implications of BCG being classified as a hazardous medication and why this is now becoming a major issue in Urology. The other BCG saga, namely the worldwide shortage of intravesical BCG, is a topic to be considered elsewhere.

There is growing concern of the risks to health care providers from the administration of hazardous medications. BCG is on the NIOSH hazardous medication list. In December 2019, USP 800 Guidelines expands controls for the protection of workers from hazardous drugs and are expected to be widely adopted by health care organizations.[3] USP uses NIOSH to identify hazardous drugs. USP 800 outlines the requirements for mixing hazardous drugs and mostly refers to chemotherapeutic agents but by default includes BCG as an anti-cancer agent. USP 797 will also be formally upgraded in December 2019. Compounding pharmacy sterile drug mixing is regulated under USP 797 and covers medications such as total parenteral nutrition, other drug infusions mixed in patient specific concentrations.[4] USP 797 Guidelines focus on facility practices to prevent harm resulting from a contaminated or improperly prepared compounded sterile preparation.

The USP 797 regulatory environment, in particular, has changed because of the well-publicized contamination and patient harm from so called "compounding pharmacies". These "compounded sterile preparations" are not mass-produced and are usually mixed from ingredients in specific doses for an individual patient. Since BCG is considered hazardous and this hazardous product must be prepared before administration these pharmacy centric USP guidelines are now being brought into Urology practices.

It appears that BCG may have been inappropriately classified as a hazard to the health care workers by NIOSH using criteria noted previously. The NIOSH primary process is to review package inserts from the FDA website.[5] This in turn drives USP recommendations which in turn drive regulations by local pharmacy groups, health departments and others. NIOSH lists BCG as the only "non-antineoplastic agent" listed out of nearly 120 hazardous drugs.[1] The carcinogenicity of BCG has never been questioned. Concerning fetal or reproductive risks, nearly every other agent on the NIOSH hazard list are FDA pregnancy classification D or X, with the curious exception of two antineoplastics (dacarbazine and ziv-aflibercept) being listed as FDA pregnancy Classification C, the same as BCG.

This hazard classification of BCG has resulted in a series of unintended consequences in Urology. USP 797 and 800 requirements for BCG preparation and administration mandate BCG be handled just like a potentially cancer inducing chemotherapeutic agent. The risks of the immunotherapy agent BCG to the health care provider does not appear to warrant the same handling as does cytotoxic chemotherapy. NIOSH does call out BCG specifically with the following footnote but maintains BCG is a hazardous medication:

> BCG, although classified as a vaccine, is used in the treatment of certain cancers. BCG should be prepared with aseptic techniques. To avoid cross-contamination, parenteral drugs should not be prepared in areas where BCG has been prepared. A separate area for the preparation of BCG suspension is recommended. All equipment, supplies, and receptacles in contact with BCG should be handled and disposed of as biohazardous. If preparation cannot be performed in a containment device, then respiratory protection, gloves, and a gown should be worn to avoid inhalation or contact with BCG organisms.[1]

The American Urological Association (AUA) and the Society of Urology Nurse Association (SUNA) have previously prepared a white paper on intravesical BCG administration and suggested the product be prepared under a hood (*only if available*) and described the use of personal protective clothing (PPE).[6] All procedures outlined in this white paper are reasonable with good urologic care and consistent with this NIOSH statement. The pending USP Chapters will regulate the entire process from preparation to patient administration in a much more rigid fashion.

Adverse events from exposure to a health care provider administering intravesical BCG cannot be easily identified in any source that documents such exposures. Health care worker exposures from the use of BCG for percutaneous inoculation from broken skin and needle sticks have been reported without any long-term consequences noted. It is unclear if any health care provider has been harmed in the process of administering BCG since its approval for intravesical use in the US in the early 1990's.

Of interest, many urology centric medications beyond BCG are also on the NIOSH list of hazardous drugs in the health care setting. This list includes, for example, medications used to treat prostate cancer such as the injectable LHRH analogues leuprolide, triptorelin and others listed as "reproductive hazards" with specific storage requirements mandated to reduce exposure to health care workers. There is no disagreement that the safety of patients and health care providers is of paramount importance. However, it seems that a review of both the NIOSH and by default the USP 800 hazardous drug listings as they relate to urologic care deserve to be reevaluated.

We are also dealing with a terminology problem. In terms of USP 800 there is confusion between the terms "compounding" and "administration". The USP 800 regulations refer to the process of drug compounding. According to the FDA "Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling".[7] Based on this definition BCG is not a compounded drug but is being treated as such in these Chapters. It should be clear that reconstituting a medication not considered compounding but rather administration. There is hope that USP Chapter 797 may help clarify this terminology.

If USP 800 is fully implemented and enforced there are significant implications for Urology practices. These USP Chapters require BCG be compounded in C-PEC (containment primary engineering control) located in either

a negative pressure buffer room or a ventilated hood device designed to minimize worker and environmental hazardous drug exposure. The unintended consequences of classifying BCG as a hazardous and compounded drug has a major impact on urology care as these devices are not considered as a routine part of a urology care facility.

If concerns remain over significant health care worker to BCG exposure, these can be mitigated by a variety of closed-system drug transfer devices (CTSDs). These devices are already in widespread use in the pharmacy setting and used by personnel administering cytotoxic drugs at the bedside. Several years ago, consistent with AUA/SUNA recommendations and since we did not have an office hood, our department adopted one of these closed needleless systems. This was a patient and staff friendly approach to minimize any potential exposures. The BCG administration is in a completely closed system from reconstitution through the use of a catheter adapter for the intravesical instillation. The use of a completely closed system for reconstituting and administering intravesical BGC continues to be questioned at our institution and by state regulators.

Many regulatory agencies and institutions have mandated USP 800 compliance with the December 1, 2019 deadline. This includes adoption of the NIOSH hazardous drug listing. If there is any doubt about what might be coming I refer you to the USP "Ready for 800" web site (https://www.readyfor800.com/) that states: "The enforcement of USP standards depends on local, state, and federal regulatory agencies. Accrediting bodies like The Joint Commission survey for compliance with USP compounding standards. The CMS State Operations Manual, which is used by surveyors to ensure that all of the Conditions of Participation are being met, includes references to USP standards".

Our Department has already been significantly impacted by these evolving regulations in terms of patient convenience and costs. As per our hospital administration and state regulatory authorities we were directed to alter our BCG administration to pre-emptively comply with USP 800. These strict USP compounding guidelines require us to use a remote pharmacy facility with a high-level containment hood to reconstitute the BCG and employ strict post administration room cleaning procedures. All of this has greatly increasing the cost of bladder cancer treatment and has taken a 15-minute office visit into a nearly two-hour experience with ordering and then waiting for the BCG delivery. I have been in communication with the AUA leadership since last summer concerning these changes and specifically how our practice has been impacted.

Does this overview provide the answer to is BCG is a hazardous drug? While I leave it to the reader to make their own opinion, I hope this discussion gives some insight into this evolving regulatory landscape. These USP 797 and 800 Chapters are primarily written for pharmacy operations and will now potentially impact many urology practices. Some changes may be unnecessary based on the perceived hazards of BCG. The AUA will be engaged in further discussions with many of the agencies noted here. A dialogue between the FDA, NIOSH, USP, pharmacy groups, urology nursing professionals and urologists is urgently needed before USP 797 and 800 become enforceable later this year.

Our specialty should remain hopeful that there will be a reasonable reclassification of these hazardous medications. The unintended consequences of the USP Chapters should be addressed. All stakeholders must agree upon reasonable, cost effective, convenient and a safe approach to administering intravesical BCG. A consistent and reasonable message to all parties including patients, pharmacy staff and providers concerning the intravesical use of BCG is needed. We should place a high value on the significant utility of BCG in controlling bladder cancer rather than promote the fear of BCG as a hazardous drug.

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References

1. https://www.cdc.gov/niosh/docs/2004-165/
2. NIOSH [2016]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. By Connor TH, et al. Cincinnati, OH: U.S. DHHS (NIOSH) Publication Number 2016-161 (Supersedes 2014-138)
3. http://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare
4. www.usp.org/compounding/general-chapter-797
5. https://dailymed.nlm.nih.gov
6. https://www.auanet.org/guidelines/intravesical-administration-of-therapeutic-medication
7. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ ucm339764.htm