Notice to Hospitals Regarding Ceftriaxone–Calcium Incompatibility: What's a Clinician to Do?

Over the past 20 years, ceftriaxone has been used extensively in Canada as the workhorse third-generation cephalosporin. The recognized toxic effects of ceftriaxone include biliary sludging and biliary or renal lithiasis, both of which are uncommon in adults. Incompatibility with lactated Ringer's solution resulting in precipitates has also been recognized.[1] Reports of neonatal deaths associated with ceftriaxone–calcium precipitates led the manufacturer and the US Food and Drug Administration (FDA) to make changes to the product monograph in 2007.[2,3] These changes generated considerable concern, discussion, and consternation among pharmacists.[3-6] During summer 2008, Health Canada issued a "notice to hospitals" regarding ceftriaxone; this, combined with a simultaneous worldwide shortage of cefotaxime, brought the issue to the forefront again.[7]

The recommendations issued by Health Canada in July 2008 were as follows:

- For patients younger than 10 weeks of age, IV ceftriaxone and IV calcium-containing solutions should not be administered within 5 days of one another.
- For all other patients, IV ceftriaxone and IV calcium-containing solutions should not be administered within 48 h of one another.
- Ceftriaxone and calcium-containing solutions, including calcium-containing solutions for continuous infusion, such as parenteral nutrition, should not be mixed or co-administered to any patient, regardless of age, not even via different infusion lines at different sites.

Over the past year, hospital pharmacists have had to assess and interpret, as well as implement processes to address, the changes in the ceftriaxone product monograph and warnings from the United States. Limitations on the use of ceftriaxone in neonates have been implemented on the basis of the severity of the case reports and the risk factors in this population.[2,8,9] However, the requirement for a 48-h avoidance window for the general adult population has been especially difficult for pharmacists and allied health professionals to implement. The difficulty in accepting the Health Canada notice to hospitals arises from the lack of similar reports of toxic effects in adults, the paucity of adult risk factors, and the arbitrary nature of the 48-h avoidance window in adults (representing 5 half-lives of the drug in adults). Adding to the confusion, a recent review on ceftriaxone–calcium interactions suggested that the half-life of ceftriaxone is longer in elderly patients than in younger adults, which may necessitate the avoidance of ceftriaxone in those with advanced age.[10] However, to date, there are no data to support the extrapolation of the warning regarding avoidance of concomitant ceftriaxone–calcium therapy in any patient population other than neonates. The concern expressed by many with respect to the combination of ceftriaxone and calcium is the ambiguity and application of the 48-h avoidance window. In practice, many institutions have reported great difficulty in developing policies regarding this 48-h time frame, and questions have arisen during amendment of institutions' ceftriaxone administration policies: What is the level of risk for adult patients? Are there any data to support this risk in the adult patient population? Does ceftriaxone bind to physiologic calcium? When does the stopwatch start and stop for this avoidance window, and is the time counted by the second, minute, or hour? Who is responsible for implementing a 48-h avoidance policy: the pharmacist, nurse, or physician?

These issues were compounded this past summer by a global shortage of cefotaxime. Soon after the cefotaxime shortage was announced, Health Canada released the notice to hospitals regarding ceftriaxone.[7] Canadian pharmacists hoping that Health Canada would have a perspective different from that of the FDA were disappointed. In response to a letter of inquiry about a mechanism to discuss our concerns with Health Canada, the department reiterated its role as the regulator, with a mandate that includes communicating patient safety issues (Diane Brideau-Laughlin, Drug Information Pharmacist, The Moncton Hospital; personal communication, March 12, 2009). Health Canada also noted that its role does not include decision-making on the choice and administration of a drug to individual patients (i.e., "the practice of medicine") and that the ultimate decision to use a drug rests with the physician and his or her knowledge about the safety data. Subsequently, in February 2009, representatives of Health Canada and several hospital pharmacists (including the person who wrote the letter of inquiry mentioned above) met to gain a better mutual understanding of the concerns of hospital pharmacists and the regulatory constraints of Health Canada. Unfortunately, the warnings will remain in place. As such, each of our hospitals has had to make decisions on how to respond to the Health Canada advisory regarding concomitant administration of ceftriaxone and calcium to adult patients.

How have pharmacists and health care institutions responded? Some have changed IV administration policies, switched to a different cephalosporin, or avoided the use of ceftriaxone in high-risk populations (e.g., patients receiving total parenteral nutrition or those receiving care in the intensive care unit). Others have discussed the issue with colleagues at both the clinical and administrative levels and have obtained support to continue using ceftriaxone in light of more than 20 years of clinical experience in millions of adult patients worldwide and

the lack of any data to support the occurrence of this toxic effect in adults. Is there a single correct response? No. The range of responses is appropriate, given the data currently available.

The bottom line is that pharmacists and physicians must evaluate the data to ensure that we are neither putting our patients at risk of toxic effects nor denying them the benefits of a drug with a proven track record of efficacy and safety.

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Alfred Gin, BScPharm, PharmD, FCSHP
Pharmaceutical Services
Health Sciences Centre
Winnipeg, Manitoba

Sandra Walker, BScPharm, PharmD, FCSHP
Pharmacy
Sunnybrook Health Sciences Centre
North York, Ontario

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