

Reducing Adverse Events and Hospitalizations Associated with Drug Interactions

A drug-drug interaction is a pharmacokinetic or pharmacodynamic influence of one drug on another, which can reduce the effectiveness of one or both of the interacting drugs or can lead to toxic effects.¹ It is estimated that such drug interactions cause up to 2.8% of hospital admissions,² and they can lead to serious adverse outcomes for patients. One drug combination that has resulted in death involved an interaction between transdermal fentanyl and Kaletra (a medication used in HIV post-exposure prophylaxis). The details of this incident were described in a previous ISMP Canada Safety Bulletin (<http://ismp-canada.org/download/safetyBulletins/ISMPCSB2008-03HIVPEP.pdf>).³

Challenges in Preventing Drug-Drug Interactions

Harmful drug-drug interactions are, in theory, largely preventable. For most drugs, a number of therapeutic alternatives are available, allowing avoidance of significant interactions. In practice, however, clinicians' recognition and detection of drug interactions is not optimal. For instance, in a study of 263 physicians practising in a large healthcare system, only 54% of contraindicated drug interactions were recognized.⁴ The continually increasing number of drugs and hence drug interactions makes it virtually impossible for healthcare practitioners to keep up with new knowledge and heightens the risk that significant drug interactions will be overlooked.

One solution to over-reliance on human memory for detecting drug interactions has been the development of computerized drug interaction detection systems;

however, studies evaluating the use of such systems in real-world pharmacy settings have identified opportunities for improvement. For example, one study found that these systems may fail to detect up to a third of drug interactions while frequently alerting pharmacists to trivial issues.⁵ Researchers have also found that the number of clinically insignificant alerts leads to a phenomenon called alert fatigue (whereby practitioners become desensitized to the alerts), which may in turn result in significant interactions being missed.⁶

Clinical Significance of Drug-Drug Interactions

One of the fundamental reasons that computerized drug interaction detection systems lack sensitivity and specificity in identifying drug interactions has been the lack of high-quality evidence evaluating the clinical significance of drug interactions. However, a growing body of research is starting to fill this gap. By utilizing pharmacoepidemiological methods, with data from various databases (such as the Ontario Drug Benefit prescription claims database), recent studies have clearly demonstrated a significant association between specific drug interaction pairs and hospitalizations for adverse events.^{6,7} Examples include increased risks of hospitalization due to (1) hypoglycemia caused by concomitant use of cotrimoxazole and glyburide and (2) digoxin toxicity caused by concomitant clarithromycin and digoxin.⁶

A summary of pharmacoepidemiological studies from Ontario involving drug interaction pairs that have been

shown to increase the rate of hospital admissions among elderly patients can be found on the ISMP Canada website at http://www.ismp-canada.org/beers_list/downloads/Drug-DrugInteractions.pdf. Healthcare practitioners are encouraged to review these specific drug interactions and the related adverse events.

Conclusion

Drug–drug interactions represent a potentially serious problem that can result in preventable adverse drug events and use of scarce healthcare resources. A growing body of high-quality studies is demonstrating an increase in hospital admissions related to specific drug interaction pairs. Healthcare practitioners who familiarize themselves with the impact of the specific drug interactions summarized at the ISMP Canada website can use this information to help reduce adverse

events and hospitalizations by identifying patients at risk and intervening as appropriate.

In addition, ISMP Canada will be undertaking a pilot project with Ontario community pharmacists to reduce the occurrence of the drug interaction pairs that have been associated with hospitalizations. Pharmacists will be supported with tools and educational resources throughout the project, which will be integrated with the Ontario Ministry of Health and Long-Term Care Pharmaceutical Opinion Program (a professional pharmacy service that reimburses pharmacists for interventions to address drug-related problems). Practitioners who are interested in more information about this project, whether in Ontario or elsewhere in the country, are encouraged to contact ISMP Canada at info@ismp-canada.org.

Overfill Needs to be Taken into Account for IV Chemotherapy

More than 1100 Canadian patients may have received lower doses of cyclophosphamide or gemcitabine than intended because of miscommunication between a supplier and several hospitals that utilized its services (<http://www.cbc.ca/news/canada/story/2013/04/02/chemotherapy-dilution.html>). The impact on patients is unclear but is under investigation.

The chemotherapy was part of therapeutic regimens for patients with breast and lung cancer, as well as lymphoma and leukemia. Solutions of the drugs were prepared by the supplier in ready-to-use IV bags, but the bags held a greater volume of diluent than stated on the label, a situation known as overfilling. The amount of overfilling is thought to have ranged from about 3% to about 20%. For reasons that have not yet been revealed, the supplier and the hospitals did not have a common understanding of the total amount of overfill after the chemotherapy additive was added to commercially available IV bags, which have an inherent overfill volume. Because of the inherent overfill, the final drug concentration in each prepared bag was less than if the exact amounts of drug and diluent solution had been added to an empty IV bag. Each bag contained the labelled amount of drug, but a lack of a common understanding of the final concentration led to some patients receiving a lower dose than intended.

Management of any overfill volume is perceived to be more critical for oncology medications than for other types of medications because the dosing of these drugs is highly specific to each individual patient and the type of cancer being treated. In the recently released International Medication Safety Self Assessment® (MSSA) for Oncology (<https://mssa.ismp-canada.org/oncology>) developed jointly by ISMP in the United States and ISMP Canada, the use of overfill was identified as a point where safeguards may be required. Specifically, the International MSSA for Oncology states the need for “a standard process to identify the overfill volume on the pharmacy label for compounded IV chemotherapy/biotherapy solutions”. An opportunity exists to create and implement national standards for labelling containers that contain overfill volume. We would very much like to hear from front-line practitioners, hospital administrators, and others with thoughts on this problem, as we work with our partners to develop recommendations for standard labelling practices.

References

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The Canadian Medication Incident Reporting and Prevention System (CMIRPS) is a collaborative pan-Canadian program of Health Canada, the Canadian Institute for Health Information (CIHI), the Institute for Safe Medication Practices Canada (ISMP Canada) and the Canadian Patient Safety Institute (CPSI). The goal of CMIRPS is to reduce and prevent harmful medication incidents in Canada.



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