

Unexpected Hypoglycemia: Consider Medication Error in the Differential Diagnosis

A recent cluster of voluntarily submitted medication incident reports in which use of insulin or an oral hypoglycemic agent led to harm in nondiabetic patients has prompted a focused review. The term “medication incident” is widely used to represent the preventable subset of potential and actual adverse drug events. It is also recognized as an alternative term for “medication error”.¹ Ten drugs accounted for 43% of all harmful medication incidents reported to ISMP Canada. Of these, insulin was second only to opioids as a leading cause of harm.² Oral hypoglycemic agents have been identified as high-alert medications, but an ISMP US survey indicated that only 23% of healthcare practitioners (nurses, pharmacists) considered them as high-alert medications.³ The purpose of this bulletin is to heighten awareness of medication incidents involving insulin and oral hypoglycemic agents.

The risk of drug-induced severe hypoglycemia (e.g., blood glucose less than 2.8 mmol/L) exists with both insulin and oral hypoglycemic agents such as those that stimulate the body’s release of insulin (sulfonylureas [e.g., glyburide, gliclazide, glimepiride, chlorpropamide, tolbutamide] and metiglinides [e.g., repaglinide and nateglinide]).⁴ The incidents reported to ISMP Canada involving these medications are summarized in Table 1. Although it is impossible to

Table 1. Reported medication incidents* involving insulin and oral hypoglycemic agents that stimulate insulin release

Category of medication	Total no. of reports	No. of reports categorized as harmful, [†] including death
All insulins	811	88 (10.9%)
Oral hypoglycemic agents that stimulate insulin release (sulfonylureas and metiglinides)	149	10 (6.7%)

* ISMP Canada’s voluntary reporting program has been in place since 2001. A total of 19,508 incident reports (including reports of near misses) have been collected since the program’s inception. Of these, 886 (4.5%) were reported to have resulted in harm to patients, including death.

† As defined by the Canadian Medication Incident Reporting and Prevention System (CMIRPS).⁵

infer or project the absolute occurrence rate of specific incidents on the basis of voluntary reports, these data are useful to indicate trends and areas of concern.

The following examples of voluntary reports involving harm are shared:

- A nondiabetic patient received 50 units of insulin subcutaneously (0.5 mL) instead of the intended heparin 5,000 units (0.5 mL); this incident led to serious harm.
- A nondiabetic adult patient being treated for dementia was experiencing recurrent hypoglycemia. An endocrinologist was consulted who ordered blood tests to rule out the presence of hypoglycemic medications; the results came back positive. Follow-up investigations by the pharmacy led to the conclusion that the sulfonylurea glimepiride had been dispensed instead of galantamine.
- An elderly nondiabetic nursing home resident suddenly became tremulous. She was transferred to hospital after becoming unresponsive. In hospital, she was treated for hypoglycemia and admitted. Blood tests confirmed therapeutic levels of glyburide, a drug that had not been prescribed for her. This information was communicated to the nursing home. A few days after returning to the nursing home, the patient was again found unresponsive and was readmitted to the hospital for treatment of hypoglycemia. Although her hypoglycemia was treated, she died several days later. Follow-up autopsy identified a therapeutic level of glyburide in her blood and concluded that a medication error had probably occurred repeatedly.
- In two unrelated case reports, patients received glyburide instead of prednisone from their community pharmacies. Both patients took the glyburide for several days, which led to severe hypoglycemia. In one case, the error was recognized when the patient presented to a local hospital emergency department and a pharmacist conducted a medication review. The patient required treatment and monitoring, and

the community pharmacy was notified of the error. In the other case, the error was not recognized until after admission. Despite intravenous administration of dextrose 50% and admission to the intensive care unit, the patient died. In both cases, the containers were labelled as prednisone, and the medication errors were discovered only after inspection of the tablets.

These cases illustrate the importance of considering the possibility of a medication error when hypoglycemia occurs unexpectedly. Numerous medications can cause hypoglycemia; “however the predominant causes of drug-induced hypoglycemia, even in nondiabetic patients, are the drugs used to treat diabetes.”⁶ Cases of unexpected hypoglycemia due to the inadvertent administration of insulin or an oral hypoglycemic agent to nondiabetic patients have been reported in literature.⁶⁻¹³ It has also been highlighted that patients who were admitted to hospital for treatment of hypoglycemia and who denied any use of a hypoglycemic agent had received such medication inadvertently.^{11,13} Although all of the case reports highlighted here involved the inadvertent administration of a hypoglycemic agent to nondiabetic patients, medication errors can lead to hypoglycemia in diabetic patients as well.^{7,14,15}

The cases described suggest preventative strategies for error-induced harm from insulin and oral hypoglycaemic agents. In the first case, insulin was substituted for heparin. Underlying factors contributing to mix-ups between insulin and heparin include the fact that both of these medications are dosed in units, they are available in similar formats (e.g., 10 mL multidose vials), and both may be stored in patient care areas and may be placed in close proximity to one another (e.g., atop a medication cart).^{6,7} In the glimepiride and galantamine mix-up, the intended drug (glimepiride) was stored beside the galantamine in the pharmacy. In one of the mix-ups between glyburide (Diabeta) and prednisone (Deltasone), the drugs were also stored side by side in the pharmacy. Other reported substitution errors have included glyburide for oxybutynin (Ditropan), glyburide for lorazepam, and chlorpropamide for chlorpromazine.^{7,9,10,12} Preventative strategies include:

- Segregate insulin in storage areas. Specifically, do not store insulin vials on top of medication carts or on counters in medication rooms.

- Consider use of 5,000 unit single-dose ampoules of heparin or prefilled syringes for subcutaneous administration whenever possible.
- Manage oral hypoglycemic agents as high-alert medications. For example:
 1. Review how oral hypoglycemic agents are stored in the pharmacy and ensure they are optimally stored for differentiation.
 2. Dispense patient-specific unit doses of these agents whenever possible.

An overview of submitted medication incident reports involving insulin, the underlying causes of these incidents, and the resulting recommendations were highlighted in a previous ISMP Canada bulletin.¹⁴

Although prevention strategies are paramount, a significant finding from this review is the identification of missed opportunities to reduce the degree of harm (or the recurrence of harm) associated with medication incidents involving hypoglycemic agents. Early identification of an error involving insulin or an oral hypoglycemic agent can provide a window of opportunity to mitigate harm and also identify and eliminate the underlying cause(s) of the error to prevent recurrence. It is essential to **consider the possibility of a medication error, in the differential diagnosis, whenever unexpected hypoglycemia occurs.**

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ALERT: Zytram XL Name Looks and Sounds Like Zyban

ISMP Canada has received a report of concern about a newly marketed product with the brand name Zytram XL. Zytram XL is the brand name for tramadol hydrochloride controlled release tablet. Zytram XL looks and sounds like a brand name for bupropion hydrochloride, Zyban. Zytram XL is an opioid analgesic, whereas Zyban is a smoking cessation aid. With both products available in 150 mg tablets (Zytram XL is also available in 200 mg, 300 mg, and 400 mg controlled release tablets), the reporter expressed concerns about the possibility of an inadvertent mix-up. Subsequently, ISMP Canada received a second report in which a prescription for “Zytram XL 150 mg po once daily” was processed as “Zyban 150 mg po once daily”. ISMP Canada has notified Health Canada and Purdue Pharma, and both organizations are following up on these reports.

The following strategies are suggested as interim measures to reduce the risk of a mix-up: use the generic name (in addition to the brand name where applicable), clarify the indication of the drug with the patient and the prescriber if necessary, clearly distinguish the two drugs in the product selection screen of pharmacy order entry systems, and avoid stocking these items in close proximity in the pharmacy.

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ISMP Canada is a national voluntary medication incident and ‘near miss’ reporting program founded for the purpose of sharing the learning experiences from medication errors. Implementation of preventative strategies and system safeguards to decrease the risk for error-induced injury and thereby promote medication safety in healthcare is our collaborative goal.

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 can also be contacted by e-mail: cmirps@ismp-canada.org. 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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