The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national nonprofit agency established for the collection and analysis of medication error reports and the development of recommendations for the enhancement of patient safety.

**Desmopressin Incidents Identify a Need to Evaluate Monitoring Protocols**

The deaths of 2 children described in a Canadian publication that appeared in 2004 were associated with the use of desmopressin in managing acute central diabetes insipidus after neurosurgical resection of non-malignant brain tumours.1 Researchers in the United Kingdom reviewed 103 pediatric cases in which central diabetes insipidus was treated with desmopressin. The diabetes insipidus occurred most frequently following neurosurgical procedures for craniopharyngioma. Of the total number of cases reviewed, 33 patients had one or more episodes of water retention and hyponatremia and 2 deaths resulted from water intoxication.2 A case involving the death of a young adult after neurosurgery was recently reported to ISMP Canada and is summarized below. Although the issues related to fluid and electrolyte imbalance and corresponding replacement therapy are complex and beyond the scope of this bulletin, this case illustrates that system safeguards are needed to ensure appropriate management of fluid and electrolyte balance when desmopressin therapy is required.

**Case Report**

A previously healthy young adult underwent neurosurgery for resection of a non-malignant brain tumour. After the operation, the patient experienced electrolyte imbalance, including hypernatremia, and diabetes insipidus was diagnosed. After an initial dose of desmopressin was administered intravenously, the patient’s serum sodium level returned to within normal limits and urine output decreased as intended. About 24 hours later, the patient’s urine output had increased, and a second dose of desmopressin was given intravenously. In addition, the patient continued to receive hypotonic saline IV solution to replace urine losses. A few hours after the second dose, the patient experienced a seizure. Serum electrolyte levels were checked, and sodium was found to be in the low normal range. During the night, when urine output increased again, a third IV dose of desmopressin was administered. When the results of laboratory tests were reviewed in the morning, the serum sodium was slightly below normal. The IV solution was changed to dextrose 5%,* and replacement of urine losses continued. Later that morning, the patient reported nausea and was given dimenhydrinate. A few hours later, the patient was unresponsive, with fixed and dilated pupils. At that time, the serum sodium level was well below normal, and the patient had a positive fluid balance of several litres measured over the preceding 24 hours. Despite several days of treatment in an intensive care unit, the patient’s neurologic status did not improve, and life support was withdrawn.

**Background**

In central (also called cranial) diabetes insipidus, secretion of antidiuretic hormone (ADH) from the pituitary gland is absent. This in turn leads to a water metabolism disorder characterized by hypotonic polyuria (very high urine output with reduced osmolality [i.e., reduced proportion of solutes to fluid]). Central diabetes insipidus may be transient, occurring after neurosurgery or other trauma to or near the pituitary gland, or it may be chronic.

Desmopressin acetate, a synthetic analogue of the natural pituitary hormone ADH, is used in the management of central diabetes insipidus. Administration of desmopressin results in increased resorption of electrolyte-free water, decreased urinary flow, and increased urine osmolality. IV administration of desmopressin leads to prompt onset of antidiuretic action, and the drug has a long and variable duration of action.4 Fluid administration combined with desmopressin therapy must be managed carefully to avoid the complication of dilutional hyponatremia or water intoxication (excess electrolyte-free water).5,7 Hypotonic solutions should not be administered intravenously to patients whose serum sodium level is below normal or when laboratory results indicate a trend towards a below normal level.

Monitoring of fluid and electrolyte status is essential to the care of all postoperative patients; however, for neurological patients who may have compromised central ADH function, observation of the rate of change in fluid and electrolyte status is critical.7 Minor increases in cerebral electrolyte-free water may lead to disproportionately large increases in intracranial pressure due to swelling of brain cells.6,7 It is critical to maintain the sodium and free-water balance to prevent increased intracranial pressure and brain herniation.5,7

**Contributing Factors**

The following factors were identified as possibly contributing to the sentinel event described in the case report:

- Continued IV administration of hypotonic fluid and desmopressin after the serum sodium had normalized and the ability of the kidneys to concentrate urine was restored

* Of note, once infused, dextrose is rapidly metabolized and infusions such as dextrose 5% become hypotonic.5,6

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**ISMP Canada Safety Bulletin**

Volume 8, Issue 1  March 3, 2008
• Acute shift in serum sodium, from a state of hypernatremia to a state of hyponatremia

Recommendations

ISMP Canada suggests the following measures to reduce the likelihood of preventable harm with desmopressin therapy:

• To facilitate early diagnosis of central diabetes insipidus, develop and use standardized order sets (preprinted or electronic), including monitoring parameters, for postoperative neurosurgical patients.
  ○ If the diagnosis of central diabetes insipidus is made early (e.g., when there is mild elevation of serum sodium), desmopressin treatment alone may be sufficient. Such monotherapy reduces the therapeutic complexity that can occur when desmopressin is combined with fluid management to correct the serum sodium level.
  ○ During postoperative transfer, include debriefing of the multidisciplinary team about the anticipated complications, such as central diabetes insipidus, to ensure that monitoring and treatment guidelines are understood. Continue to include this information in all practitioner hand-offs and during multidisciplinary rounds until no longer applicable.

• Include the cumulative fluid balance (intake and output) from the intraoperative period when assessing fluid balance in the postoperative period, as substantial diuresis due to intraoperative hydration can occur postoperatively without central diabetes insipidus (or after resolution of transient diabetes insipidus).

• Develop and use standardized order sets (preprinted or electronic) for desmopressin to ensure optimal monitoring.
  ○ Include frequent monitoring of parameters (laboratory serum and urine osmolality [or urine specific gravity], serum and urine electrolytes, and urine output) and specify the duration of monitoring.
  ○ Ensure that urine output alone is not used to determine whether subsequent doses of desmopressin are required.
  ○ Prompt laboratory turn-around times are critical. In addition, when reviewing the laboratory results, consider the time that has elapsed since the sample was taken.

• Re-evaluate the rate and choice of IV solutions and the need for each desmopressin dose in the context of laboratory trends. Exercise extreme caution in the use of hypotonic IV fluid replacement.

• Develop documentation procedures to ensure that critical information, including trends, are readily available and monitored by all practitioners caring for the patient.

• Carefully monitor patients who are receiving desmopressin for early signs and symptoms of hyponatremia and water intoxication, such as headache, nausea or vomiting, restlessness, drowsiness, lethargy, disorientation, confusion, irritability, abnormal mental status, or seizure activity.3 (Cushing’s triad [elevated systolic blood pressure with widening pulse pressure, bradycardia, altered respiratory rate and rhythm] represents late signs of increased intracranial pressure and may suggest imminent brain herniation requiring immediate intervention. 8,9)

• Engage family members in monitoring behavioural cues—subtle changes may be more readily identified as abnormal by family members than by health care providers.

• Ensure that drug information protocols, medication administration manuals, and other available references clearly identify the signs and symptoms of hyponatremia, which can lead to seizures, coma and death.

While neurosurgical patients represent a small subset of patients requiring desmopressin, the importance of monitoring fluids and electrolyte balance are not limited to this population. It is hoped that this bulletin will raise awareness of the potential for harm related to fluid management with desmopressin and that consideration will be given to implementing the described recommendations to enhance prescribing and monitoring processes with this drug.

ISMP Canada gratefully acknowledges the expert review of this bulletin provided by (in alphabetical order):

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FDA Alert Requests that Prescribing Information for Desmopressin Be Updated with New Information

Following a review of 61 postmarketing cases of hyponatremia-related seizures associated with administration of desmopressin, the US Food and Drug Administration (FDA) issued an alert and asked manufacturers to update the prescribing information for this drug to include important new information about severe hyponatremia and seizures.

The FDA advises: “Certain patients taking desmopressin are at risk for developing severe hyponatremia that can result in seizures and death. Children treated with desmopressin intranasal formulations for primary nocturnal enuresis (PNE) are particularly susceptible to severe hyponatremia and seizures. As such, desmopressin intranasal formulations are no longer indicated for the treatment of primary nocturnal enuresis and should not be used in hyponatremic patients or patients with a history of hyponatremia. PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatremia.”

The complete alert is available from: http://www.fda.gov/cder/drug/InfoSheets/HCP/desmopressinHCP.htm
**Alert: Recent Change in Rituximab (Rituxan®) Labelling Leads to Reports of Mix-ups**

ISMP Canada has received 6 reports regarding the new labelling for rituximab (Rituxan®). Four of these reports involved mix-ups between rituximab and trastuzumab (Herceptin®) vials, which fortunately were caught in the pharmacy before dispensing. Two reports identified look-alike concerns with these vials. The manufacturer of both products, Hoffmann-La Roche Ltd., recently changed the rituximab label from orange with black print to mainly white with dark blue print and orange print for the dose. (Figures 1 and 2; ISMP Canada thanks the reporter who submitted photographs with their report).

Rituximab is used in the treatment of non-Hodgkin’s lymphoma and rheumatoid arthritis, whereas trastuzumab is used, in conjunction with other medications, for the treatment of breast cancer. Both rituximab and trastuzumab require refrigeration, and they are likely to be stored side by side (e.g., if storage is in alphabetical order by generic name). Even though the trastuzumab is supplied as a powder, once reconstituted, the vial may be stored in the refrigerator without the original outer package.

ISMP Canada has notified the manufacturer and Health Canada. Hoffmann-La Roche Canada has indicated that the reason for the change in the rituximab label was to conform with the manufacturer’s global label format. The company noted that written notification of this change had been sent to customers and would continue to be reinforced by sales staff. In addition, a global review and revision of all product labelling is under way, with rituximab labelling scheduled for review during the summer of 2008. ISMP Canada hopes that the Hoffmann-La Roche parent company (in Switzerland) will consider these reports during the label redesign process and that development of a new label will be expedited.

In the interim, the following strategies which have been implemented by reporting facilities are suggested by ISMP Canada to reduce the possibility of error:

- Do not store rituximab and trastuzumab in close proximity to each other in the pharmacy (e.g., store on separate shelves in refrigerator).
- Consider applying auxiliary labels to enhance differentiation of the rituximab vials.
- Share this alert to inform all staff about the potential for a mix-up.

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**Figure 1.** From left to right: trastuzumab vial (440 mg/21 mL, reconstituted) and previous rituximab vial (500 mg, 10 mg/mL).

**Figure 2.** From left to right: trastuzumab vial (440 mg/21 mL, reconstituted) and new rituximab vial (500 mg, 10 mg/mL).