Desmopressin Incidents Indicate Need for Pharmacist Involvement in Development and Use of Monitoring Protocols

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INTRODUCTION

A recent *ISMP Canada Safety Bulletin*[1] described safety concerns related to fluid management and desmopressin therapy. Here, we review selected information and excerpts from that bulletin that are highly relevant to hospital pharmacists. One of the key recommendations in the bulletin was to develop a protocol for monitoring patients who require desmopressin therapy. Development of standardized protocols and predefined order sets to assist in the management of selected patient groups is a high-leverage strategy for enhancing consistency and incorporating best practices into patient care processes.

CASE REPORT

A previously healthy young adult underwent neurosurgery for resection of a nonmalignant 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days of treatment in an intensive care unit, the patient's neurologic status did not improve, and life support was withdrawn.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

Desmopressin acetate, a synthetic analogue of the natural pituitary hormone antidiuretic hormone, is used in the management of central diabetes insipidus. Central diabetes insipidus may be transient, occurring after

neurosurgery or other trauma to or near the pituitary gland, or it may be chronic. Administration of desmopressin results in increased resorption of electrolyte-free water, decreased urinary flow, and increased urine osmolality.[2] IV administration of desmopressin leads to prompt onset of antidiuretic action, and the drug has a long duration of action.[3] Fluid administration combined with desmopressin therapy must be managed carefully to avoid the complication of dilutional hyponatremia or water intoxication (excess electrolyte-free water).[4,5] Hypotonic solutions should not be administered intravenously to patients whose serum sodium level is below normal or when laboratory results indicate a trend toward a below-normal level. (Of note, once infused, dextrose is rapidly metabolized, and infusions such as dextrose 5% become hypotonic.[4,6])

Monitoring of fluid and electrolyte status is essential to the care of all postoperative patients; however, for neurosurgical patients who may have compromised central antidiuretic hormone function, observation of the *rate of change* in fluid and electrolyte status is critical.[5] Minor increases in cerebral electrolyte-free water may lead to disproportionately large increases in intracranial pressure through swelling of the brain cells.[4,5] It is critical to maintain the sodium and free-water balance to prevent increased intracranial pressure and brain herniation.[4,5]

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 nonmalignant brain tumours.[7] In addition, 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.[8]

CONTRIBUTING FACTORS

The following factors were identified as possibly contributing to the sentinel event described in the case report at the beginning of this article:

- Continued IV administration of hypotonic fluid and desmopressin after the serum sodium had normalized and the ability of the kidneys to concentrate urine had been restored.
- An acute shift in serum sodium from a state of hypernatremia to a state of hyponatremia.

SELECTED RECOMMENDATIONS SPECIFIC TO PHARMACISTS

The following are areas where pharmacists can assist in enhancing the safe use of desmopressin:

- Ensure that drug information protocols, medication administration manuals, and other available references clearly identify the signs and symptoms of hyponatremia, a condition that can lead to seizures, coma, and death.
- Participate in the development and use of standardized order sets (preprinted or electronic) for desmopressin to ensure optimal *monitoring*:
  - Ensure that the protocols 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. (Urine output alone should not be used to determine whether subsequent doses of desmopressin are required.)
  - Ensure that standardized order sets support re-evaluation of the *rate and choice* of IV solutions *and the need for each desmopressin dose* in the context of laboratory trends. (Extreme caution must be exercised in the use of hypotonic IV fluid replacement.)
- Participate in education of the multidisciplinary team about monitoring and treatment guidelines for patients receiving desmopressin. Desmopressin is used infrequently in many settings, and it may therefore be necessary to provide "just in time" in-service training when the drug is ordered.
- 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.[2] (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.[9,10])

RECENT US FOOD AND DRUG ADMINISTRATION ALERT REGARDING DESMOPRESSIN

Neurosurgical patients represent a small subset of patients requiring desmopressin, but the importance of

monitoring fluids and electrolyte balance is not limited to this population. Following a review of 61 post-marketing 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.[11]

The FDA advised, "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.

CONCLUSIONS

It is hoped that this article will heighten awareness among pharmacists of the potential for harm related to fluid management with desmopressin. As drug information and pharmaceutical care experts, pharmacists can help to enhance safeguards to reduce the potential for harm related to desmopressin use.

References

1. Desmopressin incidents identify a need to evaluate monitoring protocols. *ISMP Can Saf Bull* 2008 [cited 2008 Apr 22];8(1):1-3. Available from: http://www.ismp-canada.org/download/ISMPCSB2008-01DDAVP.pdf
2. MicroMedex Healthcare Series. DRUGDEX evaluations: desmopressin. Greenwood Village (CO): Thomson Scientific and Healthcare; 2008.
3. DDAVP nasal spray (desmopressin acetate) [product monograph on Internet]. sanofi-aventis U.S. LLC; 2007 Jul [cited 2008 Apr 7]. Available from: http://www.fda.gov/cder/foi/label/2007/017922s038,018938s027,019955s013lbl.pdf
4. Taylor D, Durward A. Pouring salt on troubled waters. *Arch Dis Child* 2004;89(5):411-414.
5. Bohn D, Davids MR, Friedman O, Halperin ML. Acute and fatal hyponatremia after resection of a craniopharyngioma: a preventable tragedy. *QJM* 2005;98(9):691-703.
6. Cook LS. IV fluid resuscitation. *J Infus Nurs* 2003;26(5):296-303.
7. Hicock L, Lewis J. Beware the grieving warrior. A child's preventable death. A struggle for truth, healing, and change. Toronto (ON): ECW Press; 2004.
8. Rizzo V, Albanese A, Stanhope R. Morbidity and mortality associated with vasopressin replacement therapy in children. *J Pediatr Endocrinol Metab* 2001;14(7):861-867.
9. Fodstad H, Kelly, PJ, Buchfelder M. History of the Cushing reflex. *Neurosurgery* 2006;59(5):1132-1137.
10. Understanding the pathophysiology and clinical implications of the Cushing reflex and other physical signs of increased intracranial pressure [Internet]. Project TOUCH and University of Hawaii, John A. Burns School of Medicine; 2001 [cited 2008 Apr 7]. Available from: http://hsc.unm.edu/touch/datasets/datasets/definitions/cushing.shtml
11. Information for healthcare professionals: desmopressin acetate (marketed as DDAVP nasal spray, DDAVP rhinal tube, DDAVP, DDVP, Minirin, and Stimate nasal spray) [Internet]. Rockville (MD): US Food and Drug Administration, Center for Drug Evaluation and Research; 2007 Dec 4 [cited 2008 Apr 7]. Available from: http://www.fda.gov/cder/drug/InfoSheets/HCP/desmopressinHCP.htm

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- through the secure web portal at http://www.ismp-canada.org/err_report.htm
- by telephone at 416.733.3131 or toll-free at 1.866.544.7672 (1.866.54.ISMPC)