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Desmopressin (dDAVP) incident signals the need for enhanced monitoring protocols

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Abstract

In this article, the authors highlight the circumstances surrounding the death of a young adult neurosurgical patient, recently reported to ISMP Canada. The incident signals the need for enhanced safeguards for patients receiving desmopressin (also known as dDAVP) and intravenous therapy. The authors present information from a recent ***ISMP Canada Safety Bulletin*** *relevant to critical care, including an outline of potential contributing factors and suggested recommendations.*

The deaths of two children associated with the use of desmopressin (also known as dDAVP) to manage acute central diabetes insipidus after neurosurgical resection of a non-cancerous brain tumour were described in a 2004 Canadian publication (Hicock & Lewis, 2004). In the United Kingdom, researchers reviewed 103 pediatric cases where central diabetes insipidus was treated with desmopressin (Rizzo, Albanese, & Stanhope, 2001). Diabetes insipidus was found to occur most frequently following neurosurgical procedures for craniopharyngioma. Furthermore, the researchers found that of the 103 cases reviewed, 33 patients had one or more episodes of water retention and hyponatremia, and two deaths resulted from water intoxication. A case involving the death of a young adult patient after neurosurgery was the focus of a recent ***ISMP Canada Safety Bulletin;*** *information from that bulletin forms the basis of this article (ISMP Canada, 2008).*

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 intravenous (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 neurological 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 (or insufficient) (Singer & Sevilla, 2003). This 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) due to the inability of the kidneys to conserve free water in the absence (or lack) of ADH. This disproportionate loss in electrolyte-free water can lead to hypernatremia, resulting in increased serum osmolality and the movement of free water from cells, which can lead to intracellular dehydration. Patients will exhibit prominent and constant symptoms of thirst if they are alert and have a normal thirst mechanism (Singer & Sevilla, 2003). The central diabetes insipidus may be transient, occurring after neurosurgery or other trauma on 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, with subsequently decreased urinary flow and increased urine osmolality (MicroMedex Healthcare Series, 2008). IV administration of desmopressin leads to prompt onset of antidiuretic action, and the drug has a long duration of action (sanofi-aventis, 2007). Fluid administration combined with desmopressin therapy must be managed carefully to avoid the complication of dilutional hyponatremia or water intoxication (excess electrolyte-free water) (Bohn, Davids, Friedman, & Halperin, 2005; Taylor & Durward, 2004). Zada, Liu, Fishback, Singer, and Weiss (2007), who reviewed patients for delayed (post-operative day seven) hyponatremia after pituitary surgery, indicate that in cases where hyponatremia occurs between days one and three post-operatively, cortisol deficiency or fluid overload should strongly be considered.

Although the issues related to fluid and electrolyte imbalance and corresponding replacement therapy are complex, and beyond the scope of this article, it is of particular interest that IV solutions containing dextrose may be labelled and considered isotonic by practitioners because their osmolarity is similar to that of blood (Taylor & Durward, 2004). Once infused, however, the dextrose can be rapidly metabolized and dextrose 5% in water (D5W)

and dextrose 3.3% and sodium 0.3% in water (2/3 and 1/3) become *hypotonic* fluids, leaving excess electrolyte-free water to move from the intravascular compartment into the interstitial and intracellular compartments (Cook, 2003; Josephson, 2004). For example, in an overview of fluid therapy in pediatrics, for every one litre of dextrose 5% in water infused, one litre of free water is added, with one-third ending up in the extracellular space and approximately two-thirds ending up in the intracellular compartment (Taylor & Durward, 2004). When hypotonic solutions are administered in combination with desmopressin, the serum sodium level may drop more rapidly than anticipated and intracellular edema can ensue. In addition, since diabetes insipidus may be transient (i.e., the body has resumed its ability to regulate fluid balance through the ability to release a sufficient amount of ADH), the continued administration of desmopressin and hypotonic fluids, to replace urine losses, for example, can lead to excessive free water retention. It has been noted that free water is necessary to cause water intoxication, desmopressin alone is not sufficient (Robson, 1996).

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 in all critical care patients. However, for neurosurgical patients who may have compromised central ADH function, observation of the *rate of change* in fluid and electrolyte status is crucial (Bohn et al., 2005). Minor increases in cerebral electrolyte-free water may lead to disproportionately large increases in intracranial pressure due to generalized intracellular cerebral edema (Bohn et al., 2005; Taylor & Durward, 2004). It is vital to maintain the sodium and free-water balance to prevent increased intracranial pressure and brain herniation (Bohn et al., 2005; Taylor & Durward, 2004).

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.
- 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 (and potentially other diagnoses of water metabolism disorders), develop and use standardized (pre-printed or electronic) order sets, including monitoring parameters, for post-operative 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 and fluid management are combined to correct the serum sodium level.
- During post-operative transfer, include debriefing of the multidisciplinary team about anticipated complications, such as central diabetes insipidus, to ensure that monitoring and treatment guidelines are understood. Continue to include this information in all practitioner changes and during multidisciplinary rounds until it is no longer applicable.
- Include the cumulative fluid balance (intake and output) from the intra-operative period when assessing fluid balance in the post-operative period, as substantial diuresis due to intra-operative hydration can occur postoperatively *without* central diabetes insipidus (or after resolution of transient diabetes insipidus).
- Develop and use standardized (pre-printed or electronic) order sets 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, take into account the time that has elapsed since the sample was taken.
- Exercise extreme caution in the use of hypotonic IV fluid replacement. (In cases where the diabetes insipidus is mild, patients who are able to drink, have unlimited access to fluids, and have a normal thirst mechanism may be able to regulate their own fluid balance (Singer & Sevilla, 2003)).
- Re-evaluate the *rate and choice* of IV solutions *and the need for each desmopressin dose* in the context of laboratory trends in consultation with the physician.
- Develop documentation procedures to ensure that critical information, including trends, is readily available and monitored by all practitioners caring for the patient.
- Carefully assess and monitor patients who are receiving desmopressin for early signs and symptoms of hyponatremia and water intoxication, for example, headache, nausea or vomiting, restlessness, drowsiness, lethargy, disorientation, confusion, irritability, abnormal mental status, seizure activity (MicroMedex Healthcare Series, 2008). (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 [Fodstad, Kelly, & Buchfelder, 2006; Project TOUCH, 2001]).
- Engage family members in monitoring the patient's behavioural cues—subtle changes may be more readily identified as abnormal by family members than by health care providers.
- Ensure that desmopressin drug information protocols, medication administration manuals, and other available

references state the signs and symptoms of hyponatremia, and specify that hyponatremia can lead to seizures, coma and death.

While neurosurgical patients are a small subset of patients who may require desmopressin, the importance of monitoring fluids and electrolyte balance are not limited to this population in critical care. Some critical care units have developed comparison charts of the various water metabolism disorders (e.g., diabetes insipidus, syndrome of inappropriate anti-diuretic hormone [SIADH] secretion) to assist staff in understanding and managing them. Although the case presented is of a post-operative neurosurgical patient, the learning may be applicable to other patient types who develop diabetes insipidus. Critical care nurses working at the bedside have an opportunity and vital role to play to identify early signs of change in patient status. Although diabetes insipidus can lead to dehydration if its treatment is not appropriately monitored, it can also lead to patient harm or death from over-hydration, as illustrated in this article. It is hoped this article raises awareness of the potential for harm related to fluid management with desmopressin and that consideration will be given to implementing the described recommendations, including monitoring processes, to enhance patient management with this drug.

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ISMP Canada gratefully acknowledges the valuable lessons learned and information reported by professionals in the Canadian health care community that can then be shared to enhance medication system safety. All ISMP Canada Safety bulletins are available from **http://www.ismp-canada.org/ISMPCSafetyBulletins.htm**

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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