Patient Safety Tip of the Week

October 25, 2016

Desmopressin Back in the Spotlight

It's been almost a decade since our March 18, 2008 Patient Safety Tip of the Week "Is Desmopressin on Your List of Hi Alert Medications?" outlined our multiple concerns about the safety of desmopressin. Last week an FDA Advisory Panel recommended approval of a desmopressin nasal spray for treatment of nocturia (Bankhead 2016). The FDA has not yet ruled on approval but usually follows the recommendations of the advisory panels.

Several desmopressin formulations, including a nasal spray formulation, are already FDA-approved. But they are approved for conditions other than the treatment of nocturia. Approved indications are the treatment of central diabetes insipidus, primary nocturnal enuresis in children, and to maintain hemostasis in patients with von Willebrand's Disease and Hemophilia A during surgery. There are no current FDA-approved drugs indicated for the treatment of nocturia.

But, in reality, we know that desmopressin is already being used off-label for the treatment of nocturia. A meta-analysis of use of desmopressin for nocturia in 2012 found five studies involving a total of 619 participants and 8 additional randomized controlled trials in a systematic review (Zong 2012). The authors concluded that "desmopressin might significantly decrease the frequency of nocturnal voids, nocturnal urine volume and nocturnal diuresis, potentially resulting in an extended duration of the first sleep period and improved sleep quality. The adverse effects of desmopressin were similar to those observed in the placebo group." Based upon those studies, some clinicians have been using desmopressin for treatment of nocturia already.

But we are very concerned about the potential adverse consequences of its use for nocturia, particularly in view of the seeming limited clinical significance of its efficacy in clinical trials. Most of the safety concerns in our March 18, 2008 Patient Safety Tip of the Week "Is Desmopressin on Your List of Hi Alert Medications?" have not changed.

The applicant to the FDA is seeking a rather broad approval of the desmopressin nasal spray for "nocturia". Remember: nocturia is a symptom of a variety of underlying conditions. Given the wide range of conditions giving rise to nocturia we can anticipate that some patients will be more prone than others to adverse consequences of this treatment.

The FDA briefing document (FDA 2016) presented to the FDA Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) summarized the clinical trials used to support the request for FDA approval. Patients recruited into the clinical trials were all age 50 or older and there were multiple exclusionary criteria. One wonders how many patients with those exclusionary conditions might ultimately be treated with the drug if it gets approved for broad use for nocturia.

First, the efficacy evidence. Enrolled patients had at least a six-month history of at least two nocturic episodes per night, on average. All received placebo during a 2-week lead-in period and then were randomized to receive either 0.75 mcg, 1.0 mcg, or 1.5 mcg of desmopressin nasal spray or placebo nightly (the second trial just randomized patients to 0.75 mcg or 1.5 mcg of desmopressin nasal spray or placebo nightly) for a 12-week treatment period. Co-primary efficacy endpoints were (1) change from baseline in the mean number of nocturic episodes per night and (2) percentage of patients with ≥50% reduction in mean number of nocturic voids per night. One of the two trials also included the Impact of Nighttime Urination (INTU) Questionnaire as a secondary endpoint. It appears that neither clinical trial included fluid intake restriction.

The FDA briefing document includes a discussion on the use of an ITT (intention-to-treat) analysis vs. a mITT (modified intention-to-treat) analysis but we won't bore you with the details. Only the 1.5 mcg dose of desmopressin was statistically superior to placebo on both co-primary efficacy endpoints. Regarding the first endpoint, there was a mean reduction of 0.3-0.4 episodes per night (from a baseline of about three nightly nocturia episodes on average) with the 1.5 mcg dose compared to placebo. Though statistically significant, the FDA briefing document questions the clinical significance of this finding. In both trials, those that achieved at least 50% reduction in mean number of nocturic voids per night compared to placebo did so only with the 1.5 mcg dose (52% vs. 33% in one trial and 46% vs. 29% in the other). The 1.5 mcg desmopressin dose decreased the INTU Overall Impact score by 2.6 points more than placebo. That point difference was statistically significant but, again, of unclear clinical significance.

On the safety side, the incidence of subjects with at least one adverse event was slightly greater in those who received active drug compared to placebo. The common adverse events occurring at a greater incidence in those treated with active drug were nasopharyngitis, urinary tract infection, hypertension/blood pressure increased, sneezing, nasal congestion, back pain, dizziness, and hyponatremia. But the incidence of serious adverse events was similar to the incidence in the placebo group. All 5 deaths occurred in those receiving active drug but it was felt that the drug did not likely contribute in at least 3 of those and was questionable in the others. Four of the 5 deaths occurred in patients age 75 and older. The incidence of subjects discontinuing due to an adverse event was slightly greater in active drug group than the placebo group. The most common adverse events leading to discontinuation in those on active drug were nasal discomfort and hyponatremia. Hyponatremia occurred with incidences of 1.1%, 0%, and 0.2% respective in the 1.5 mcg, 0.75 mcg, and placebo treatment groups. The incidence of hyponatremia with active drug appears lower among subjects younger than 65 years of age compared to those over 65 years of age.

Prior studies have looked at adverse events in patients receiving intransal desmopressin. In a report on adverse events during the use of intranasal desmopressin acetate for patients with haemophilia A or von Willebrand disease, Dunn and colleagues noted 27/40 patients experienced some clinical signs of symptoms related to the drug (Dunn 2000). Most were mild but several reported moderate-to-severe side effects, including one patient who required medical intervention for symptomatic hyponatremia. The authors suggest that side-effects may be minimized if patients adhere to instructions regarding fluid intake and composition while using intranasal desmopressin. Lose and colleagues looked at the effects of long-term (10-12 months) desmopressin use for nocturia (Lose 2004). Desmopressin was well tolerated with few males (14%) or females (10%) withdrawing due to adverse events. Most adverse events were mild (44%) or moderate (44%) in severity. Four males experienced serious drug related adverse events, (dizziness, cardiac failure, headache and vomiting, chest pain and hypertension) and one female experienced 4 serious drug related adverse events (hyponatremia, headache, nausea and vertigo). Two patients had clinically significant hyponatremia.

On the basis of the clinical trial data, you'd probably conclude that this is a drug that has a marginal clinical value (though it may be more valuable to some patients) but appears to be relatively safe. The FDA Bone, Reproductive and Urologic Drugs Advisory voted 14-4 margin that benefits of the treatment outweighed potential risks.

But we have 2 major concerns. First is that the drug would undoubtedly get used in patient populations other than those enrolled in the clinical trials. Second is that the drug is likely to be prescribed by or managed by healthcare personnel who are relatively unfamiliar with it.

The exclusion criteria in the clinical trials were diabetes insipidus, uncontrolled diabetes mellitus, congestive heart failure (New York Heart Association Class IIIV), polydipsia, uncontrolled hypertension, nephrotic syndrome, peripheral edema (>2+ pretibial edema on physical exam), history of urinary retention, neurogenic detrusor overactivity, obstructive sleep apnea, loop diuretics, glucocorticoids, and severe lower urinary tract symptoms due to benign prostatic hypertrophy, overactive bladder, or severe stress urinary incontinence. Yet the application is for approval of the desmopressin formulation for any adult with nocturia. Undoubtedly it would get used in some patient populations in whom it has not been studied.

Hyponatremia is probably the most feared potential complication of desmopressin therapy. Keep in mind that in the clinical trials, fasted serum sodium concentration was assessed on Days 1 (baseline), 15, 29, 43, 57, 71, 85, and 99 of the studies. In the real world it is not likely that there will be such frequent monitoring of serum sodium levels. And it is particularly when intercurrent events occur (such as infections) that further perturbations of serum sodium might occur in patients on desmopressin therapy.

Perhaps our most serious concern involves the patient receiving desmopressin therapy who now gets hospitalized for either an intercurrent condition or an elective procedure.

The healthcare personnel dealing with such patients on an inpatient basis are quite likely to have limited experience with and knowledge about the use of desmopressin.

We did our March 18, 2008 Patient Safety Tip of the Week "Is Desmopressin on Your List of Hi Alert Medications?" because of several reports of adverse events related to desmopressin over a short period of time. The FDA issued an alert in December 2007 (FDA 2007) about the dangers of severe hyponatremia and seizures related to desmopressin. This alert was based on their review of 61 post-marketing cases of hyponatremic seizures associated with desmopressin use, including two fatal cases. Children with primary nocturnal eneuresis (PNE) taking intranasal formulations of desmopressin are particularly susceptible to these complications so the FDA alert cautioned that the intranasal formulation was no longer indicated for treatment of PNE. It also cautioned that treatment of PNE with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid/electrolyte disturbances. And it cautioned that all desmopressin formulations should be used with caution in patients at risk for water intoxication with hyponatremia or in patients taking medications that may cause them to drink more fluids, such as tricyclic antidepressants or SSRI's. The FDA has subsequently archived that safety alert. Labelling changes were made in 2007 and a safety review in 2010 revealed no further deaths or serious adverse events.

ISMP Canada issued an alert (ISMP Canada 2008) shortly thereafter about the need for monitoring protocols in patients taking desmopressin. This followed a report of a patient who developed diabetes insipidus following neurosurgical removal of a nonmalignant brain tumor. The patient was treated with desmopressin and had numerous problems with fluid/electrolyte management and had a positive fluid balance of several liters, resulting in death presumably from water intoxication and cerebral edema. Even minor increases in electrolyte-free water have been associated with disproportionately high increases in intracranial pressure. Contributing factors in this case were continued administration of hypotonic fluids and desmopressin after the serum sodium had normalized and the rapidity of the shift from a hypernatremic state to a hyponatremic state.

And a case study in an AHRQ WebM&M (AHRQ 2008) dealt with an adverse outcome related to desmopressin. Though the WebM&M focused on the issue of "hold" orders, the case again pointed out the dangers associated with desmopressin.

Those cases point out two important reasons to identify desmopressin as a hi-alert medication. First, it is a drug that may be associated with serious, even fatal, complications. Second, it's a drug that many physicians, nurses, and pharmacists have limited experience with. Many patients now end up being admitted for an unrelated reason and staff unfamiliar with desmopressin are saddled with managing it during a hospitalization. That is exactly the circumstance where having available strict protocols and monitoring programs is a smart addition to your medication safety program.

The ISMP Canada alert recommends development and use of standardized order sets (preprinted orders or electronic order sets), including monitoring parameters, for postoperative management of postoperative neurosurgical patients to facilitate early

diagnosis and management of central diabetes insipidus. They also discuss the need for discussion of such potential complications to be a part of all hand-offs. They stress the importance of standardized order sets for monitoring patients treated with desmopressin, including the frequency with which the parameters should be monitored. Urine output, by itself, should not be used to determine whether subsequent doses of desmopressin are given. The trend in the monitored parameters may be as important as the actual numbers. The choice and rate of IV fluids and the need for desmopressin should be determined by the results of those parameters. The patients should be carefully monitored for signs or symptoms of hyponatremia or water intoxication. Besides seizures, headache, nausea, vomiting and obtundation are common symptoms of water intoxication. In addition to the standardized order sets, everyone caring for the patient should have ready access to information and protocols about the drug and the monitoring. Families, too, should be engaged in monitoring because they may pick up subtle changes in the patient before professional staff would. And it is critical that the laboratory test results be available on a prompt basis.

Though the ISMP Canada alert was aimed at neurosurgical patients, the advice is wise and most of it is also applicable to other types of patients being treated with desmopressin. Perhaps the most important initial question to ask is whether continued use of desmopressin is even indicated during the acute hospitalization. For many of it uses, particularly the bladder-related ones, there may be no reason to use desmopressin at all during the hospital stay. If it is determined that desmopressin should be continued, then the type of standardized order sets and monitoring protocols similar to those in the ISMP Canada alert should be used.

Most hospitals have included in their hi-alert medication safety programs categories of more frequently used drugs that have a narrow therapeutic index or possible severe adverse side effects and then looked at drugs within those categories that may be particularly likely to be unfamiliar to clinical staff. For example, most hospitals include anticoagulants in their hi-alert medication safety program and typically focus on coumadin, heparin, LMWH's, and antiplatelet agents. However, some have recognized that drugs like argotroban may need to be used under rare circumstances and that few practitioners have extensive experience with that drug. Therefore, they have made special attempts to make appropriate information on the less familiar drug available to practitioners and have developed standardized order sets for dealing with such drugs. The same sort of logic should apply to desmopressin and it should be addressed in your hi-alert medication safety program.

One additional concern is the potential risk that an order for desmopressin might erroneously be interpreted as an intravenous medication rather than intranasal one, potentially leading to very serious complications. One such incident where it was mistakenly given intravenously was reported by ISMP (ISMP 2009). The example given included the use of the abbreviation "IN" (for intranasally), an abbreviation that ISMP would put on a "do not use" list. ISMP notes that, in addition to being mistaken for "IV", the abbreviation "IN" can also be mistaken for "IM". ISMP suggests writing out "intranasal" or "nasally" or using "NAS" instead.

We would hope that the FDA ultimately limits the scope of the population for which intranasal desmopressin is approved. Some have stated that "nocturnal polyuria", implying the need to urinate multiple times at night, may be a more appropriate indication for use of intranasal desmopressin. But in anticipation that it will approve its use for nocturia in some capacity and knowing that some clinicians have already been using it for that purpose, we think that **all hospitals should be doing certain things**:

- Require input of an "**indication**" on your order entry system when someone attempts to order intranasal desmopressin.
- Develop **standardized order sets** to help healthcare workers who may not be familiar with the use of intranasal desmopressin. Such order sets might include automatic monitoring of serum sodium.
- Make sure the abbreviation "IN" is on your **"do not use" abbreviation list**.
- Perhaps develop **criteria for when you would even continue intranasal desmopressin for nocturia** during an acute hospitalization.
- Have **pharmacists review** all orders for intranasal desmopressin.
- Make sure all caring for the patient (doctors, nurses, pharmacists) have ready **access to information and protocols** about the drug and the monitoring.
- Add desmopressin to your **"high alert drug" list** if it's not already on it.

And for the clinician, use of desmopressin for nocturia should only be considered when other non-pharmacologic measures have been taken and when the nocturia truly impairs quality of life. Nocturia may contribute to cumulative sleep deprivation and may also increase the risk of falls in the elderly (see our June 9, 2015 Patient Safety Tip of the Week "Add This to Your Fall Risk Assessment" and our many columns on fall risk and prevention). First and foremost, remember that nocturia is a symptom and has a variety of causes. Treating the underlying cause is most important. For example, nocturia may be a manifestation of congestive heart failure. So treatment of the CHF should be primary. In a review of management of nocturia in the elderly, Osman and Chapple note that lifestyle interventions, though not widely studied on a population basis, are often used based upon both logical and anecdotal evidence (Osman 2013). Lifestyle measures included reducing caffeine and alcohol, limiting evening fluid intake, leg elevation and interventions aimed at improving sleep (e.g., exercise, and warm temperature). And when desmopressin might be considered, good communications are required, not only between physician and patient but also between physicians. Most likely it may be a urologist who recommends desmopressin but the primary care physician is usually in a better position to understand potential interactions with other medications and comorbidities. The young and the elderly are two populations that are more prone to develop hyponatremia during desmopressin treatment. Desmopressin also has a relatively long and variable duration of action. Issues of unusually long half-life or bioactivity have been implicated in some cases of adverse events related to desmopressin (Dehoorne 2006). In some cases, hyponatremia due to desmopressin may have been made more likely by a second drug, such as ibuprofen (Garcia 2003).

Desmopressin is a valuable drug for many conditions. Though it may be effective and relatively safe for treating nocturia in a relatively narrow population, expansion of its use to other patient populations may well result in unintended consequences.

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