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REVIEW

Management of Diabetes Insipidus following Surgery for Pituitary and Suprasellar Tumours

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abstract: Central diabetes insipidus (CDI) is a common complication after pituitary surgery. However, it is most frequently transient. It is defined by the excretion of an abnormally large volume of dilute urine with increasing serum osmolality. The reported incidence of CDI after pituitary surgery ranges from 0–90%. Large tumour size, gross total resection and intraoperative cerebrospinal fluid leak usually pose an increased risk of CDI as observed with craniopharyngioma and Rathke's cleft cysts. CDI can be associated with high morbidity and mortality if not promptly recognised and treated on time. It is also essential to rule out other causes of postoperative polyuria to avoid unnecessary pharmacotherapy and iatrogenic hyponatremia. Once the diagnosis of CDI is established, close monitoring is required to evaluate the response to treatment and to determine whether the CDI is transient or permanent. This review outlines the evaluation and management of patients with CDI following pituitary and suprasellar tumour surgery to help recognise the diagnosis, consider the differential diagnosis, initiate therapeutic interventions and guide monitoring and long-term management.

Keywords: Central Diabetes Insipidus; Polydipsia; Polyuria; Pituitary Adenoma; Preoperative Risk Factor; Pituitary Surgery; Arginine Vasopressin; Desmopressin; Treatment.

Pituitary adenomas are the third most common intracranial neoplasm which accounts for 10–15% of all diagnosed intracranial tumours and are frequently treated with transsphenoidal surgery (TSS), except prolactinomas.[1] Neurosurgical operations for pituitary and suprasellar tumours may result in postoperative complications due to the crucial anatomical location of these tumours. The resulting postoperative complications can manifest as anterior or posterior pituitary dysfunction, particularly sodium disturbances, due to the changes in antidiuretic hormone (ADH) secretion, which remains one of the most frequent postoperative reasons for hospital readmission.[2] The patterns of water and electrolyte disorders after TSS can be divided into either polyuria or oliguria/hyponatremia, depending on the presence of either low or high levels of ADH, respectively.[2] Some disturbances of water and electrolytes may not reach the level of clinically defined central diabetes insipidus (CDI) or syndrome of inappropriate antidiuretic hormone (SIADH). However, they may still require acute or chronic management and are generally divided into six profiles of polyuria or hyponatremia as follows: transient or sustained polyuria, immediate or delayed hyponatremia and biphasic or triphasic diabetes insipidus (DI).[2,3] CDI manifests as the excretion of large amounts of dilute urine that frequently occurs in the acute phase following surgery for pituitary adenomas, subarachnoid haemorrhage or traumatic brain injury. Nonetheless, it occurs rarely in association with large pituitary adenomas before surgical interventions. Its occurrence in this setting should question this diagnosis and point towards other diagnoses such as craniopharyngioma or granulomatous diseases.[4]

Serum sodium and osmolality levels are generally maintained within a very narrow range (within 1–2%) despite marked variations in water and salt intake and this is controlled by two mechanisms, namely arginine vasopressin (AVP) and thirst. The development of CDI after TSS for pituitary adenoma is common, but it is usually transient. Most patients who have free access to fluids and have intact thirst mechanisms can maintain normal serum sodium and normal fluid balance, as well as avoid dehydration and hypernatremia that usually result from the development of a significant water deficit. Hence, it is exceptionally vital to frequently monitor the urine output, serum sodium and daily fluid balance in all neurosurgical patients following TSS. When patients have impaired levels of consciousness due to various factors, such as sedation, or if the thirst mechanism is impaired, for example in the rare subtype of adipsic DI, they can develop significant water deficit and severe hypernatremia.[5,6]

The measurement of copeptin as a surrogate marker for AVP in the diagnostic workup of the three main causes of polyuria (i.e. CDI, nephrogenic

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DI and primary polydipsia) has revolutionised the management approach of the patients with these suspected conditions, given its stable assays, high diagnostic accuracy and high specificity.[7–10] Due to a paucity of studies comparing different treatment and monitoring strategies for acute CDI following transsphenoidal pituitary surgery, there is a general lack of clear guidelines based on grades of evidence for acute DI following TSS management. Nonetheless, there have been increasing adverse events, including death, which have been highlighted in recent years for the patients with established CDI, mainly due to a lack of knowledge among health professionals dealing with this condition.[11] Hence, there is a need to update the knowledge highlighting all the pitfalls that can lead to adverse patient outcomes.

The rationale for this review article is to present updated information regarding the frequency, predictors of occurrence, clinical presentation and diagnostic workup, including the role of measurement of copeptin, which fills an important gap that exists regarding the limitation of water deprivation test in differentiating between CDI and primary polydipsia. The therapeutic interventions for CDI will also be reviewed, including those used for treating the rare and serious subtype of adipsic DI, as well as the prognosis of CDI following TSS.

EPIDEMIOLOGY

CDI is a significant complication following pituitary surgery which has been reported in the medical literature. Transient diabetes insipidus (TDI) has been reported in 1.6–45.6% of the patients after pituitary surgery with a transnasal microsurgical approach and in 2.5–26% of those who had surgery with the transnasal endoscopic approach.[6,21] Permanent diabetes insipidus (PDI) is less common and has been reported in 0–10% of patients following the microsurgical approach and in 0–12.5% of patients following the endoscopic approach.[12,13] The evidence is inconsistent regarding whether endoscopic TSS is associated with a lower incidence of DI in comparison to microscopic TSS, with some studies showing a lower incidence while others do not.[13–15] One study investigated the DI following transcranial pituitary surgery and found the incidence of TDI and PDI to be 21.1% and 12.2%, respectively.[16] CDI is more common after craniopharyngioma surgery and has been reported in up to 90% of the patients.[17] Additionally, DI occurs in the acute phase of traumatic brain injury (TBI) in approximately 3% and 26% of cases and 15% of cases of subarachnoid haemorrhage (SAH).[18,19] CDI in the vast majority of cases of TBI and SAH is transient. Persistent CDI in the setting of TBI and SAH is usually a late manifestation of severely raised intracranial pressure and, in this context, has a considerably grave prognosis.[18–20]

PREDICTORS

Early detection of CDI can be meaningful to patient care and outcomes following pituitary surgery. DI after pituitary surgery is reported to be associated with 3.9-fold increase in patients' mortality.[21] Therefore, risk factors for CDI following pituitary surgery have been explored in several studies. The factors that may predict both transient and permanent DI include craniopharyngioma, Rathke's cleft cysts, larger tumour size, low postoperative copeptin levels and intraoperative cerebrospinal fluid (CSF) leak. Other factors that have been shown to predict only TDI include ACTH-producing adenoma, visual abnormalities on presentation, suprasellar tumour extension, gross total resection, postoperative CSF leak and first postoperative serum sodium of >145 mmol/L. In contrast, predictors of PDI only include younger age and reoperation, the former likely due to large tumour mass, while the latter due to possible injury to the neurohypophysis and/or stalk traction.[2,8,22–25] After the transcranial pituitary surgery, the degree of deformation of the third ventricle and hypothalamus as assessed by preoperative magnetic resonance imaging and postoperative haemorrhage was associated with both transient and permanent DI.[17]

Presentation and Diagnosis

CLINICAL PRESENTATION

CDI should be considered when a patient excretes large volumes of diluted urine after surgery, typically ranging in 3.5–16.8 L per day, in the presence of high or normal serum sodium and osmolality.[26] The onset of polyuria is usually abrupt and occurs within the first 12–24 hours after surgery.[27] However, later presentation (two weeks to three months after surgery) has been reported in patients with Rathke's cleft cyst.[28] The pathophysiology of this is not well understood but it has been suggested to be resulting from the release of cyst contents, causing inflammation to the infundibulum.[29]

Polyuria is the hallmark of CDI. However, not all patients with polyuria after pituitary surgery have CDI, as polyuria could result from the reactive postoperative diuresis in patients who received excess amounts of intravenous fluids during surgery. It is also essential to rule out other common causes of polyuria such as hyperglycaemia and diuretics use before labelling a patient with CDI. The classic triphasic water dysregulation is rare and occurs in approximately 1.1–3.4% of postoperative patients where transient DI, a polyuric phase occurring due to the abrupt cessation of AVP release as a result of the temporary hypothalamic dysfunction, is followed by the second phase that resembles SIADH, which is caused by the sudden release of AVP from the degenerating pituitary. Finally, depletion of AVP stores leads to permanent CDI.[30,31] The onset of polyuria is usually abrupt and occurs within the first 12–24 hours after surgery. The initial transient phase of DI happens within 1–3 days after surgery and typically lasts for 5–7 days. The second phase ensues 7–8 days postoperatively and can last 2–14 days if there is no recovery of antidiuretic hormone (ADH)-secreting neurons. The third phase occurs when DI reappears as a result of depletion of ADH stores.[32–35]

Patients with DI typically complain of persistent excessive thirst and drink to compensate for the water loss to maintain serum sodium within the normal range. However, patients with limited access to water, impaired consciousness level or impaired thirst sensation may rapidly develop signs of dehydration on physical examination in addition to hypernatremia (serum sodium >145 mmol/L) if free water loss is not replaced.[36,37]

DIAGNOSTIC WORKUP

The diagnosis of CDI postoperatively begins with the risk assessment using pre- and intra-operative predictive factors before the patient is transferred from the operation room. Excessive thirst and polyuria are the clinical features that typically trigger an evaluation for CDI.[38] Hence, careful documentation of hourly fluid intake and urine output is essential for the early identification of CDI. It is crucial to note that polyuria may not always be due to DI; as seen in cases of mobilisation of intraoperative fluids and hyperglycaemia, it can also be due to a sharp drop of growth hormone level post acromegaly surgery and the use of certain medications such as furosemide or SGLT2 inhibitors.[39] Therefore, documentation of hypotonic polyuria is essential in establishing the diagnosis of DI. Seckel and Dunger criteria to diagnose CDI rely on the presence of hypotonic polyuria (urine osmolality <300 mOsmol/kg and urine output more than 2 mL/kg/h) in addition to increased serum osmolality (>300 mOsmol/kg) after excluding other causes of polyuria, such as glucosuria.[40] In adult patients in particular, urine output of more than 250 mL per hour for two consecutive hours when supplemented with the presence of normal or high serum sodium, normal or high serum osmolality with a urine osmolality of less than 300 mOsmol/kg is highly suggestive of DI.[41] Urine specific gravity is easily assessed at the bedside and could provide a

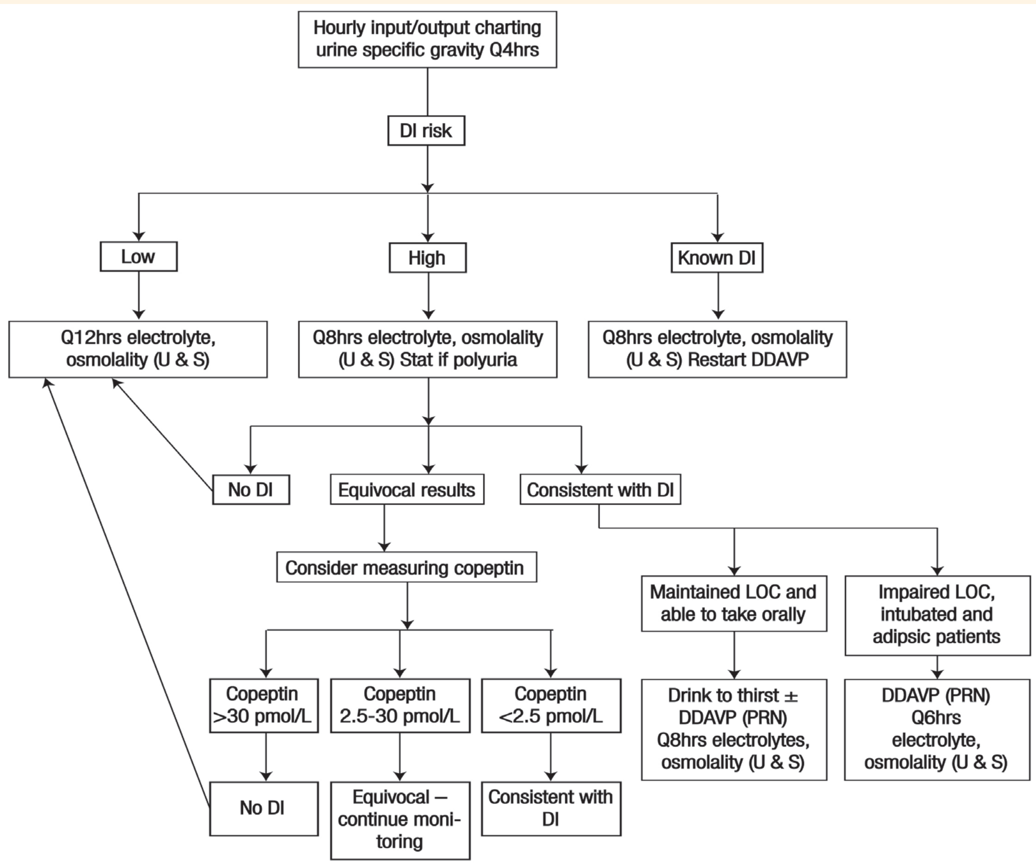

Figure 1: Post-pituitary-surgery evaluation (risk-based assessment).
DI = diabetes insipidus; U = urine; S = serum; DDAVP = desmopressin; LOC = level of consciousness; PRN = as needed.
DI Risk: Low = No risk factors; High = Any DI postoperative or intraoperative risk factors.

quicker evaluation of urine tonicity, with a value less than 1.005 suggesting low urine osmolality.[42]

However, despite the availability of these tools, the diagnosis of post-pituitary-surgery CDI could be a challenge due to several factors. First, there is a lack of universal diagnostic criteria for DI and enormous variability in the monitoring of patients following pituitary surgery. Moreover, the current diagnostic criteria may not apply to patients who are able to consume water and self-manage CDI, especially if the DI is partial. Furthermore, thin adults could have DI, but their urine output is <200 mL/h, which may delay the diagnosis. For such patients, using weight-based criteria to define polyuria (urine output of >2 mL/kg/h or >50 mL/kg/day) would be more accurate. Additionally, the frequency of monitoring electrolytes is highly variable among physicians.[43] Therefore, frequent assessment of electrolytes and osmolality in patients with a decreased level of consciousness or impaired thirst sensation is necessary for early detection of CDI.

The difficulty in diagnosing CDI, particularly in the immediate postoperative period, has led to the exploration of other ways to diagnose CDI.[44] Plasma AVP measurement has been explored; however, it could be challenging as its half-life is short (16 minutes) and the AVP is usually unstable in collected plasma samples and is affected by many factors leading to its inaccurate level.[45–47] Moreover, AVP measurement with ELISA is not usually feasible due to the small size of AVP.[48] Furthermore, AVP measurement, usually done by rapid acting insulin and requires a relatively large sample volume, is not available in a timely manner to diagnose DI as it requires a relatively long time and specialised labs to process it. For these reasons, AVP measurement is rarely useful in the diagnosis of postoperative DI.

On the other hand, copeptin is the C-terminal peptide of pro-vasopressin, co-secreted with AVP in an iso-osmolar manner, and reflects AVP level accurately. Unlike AVP, copeptin measurement is less cumbersome as it remains stable in collected plasma samples for days and its measurement is associated with less preanalytical errors.[49,50] It is highly accurate in identifying the aetiology of polyuria in the non-acute setting.[51] However, its utility in the post-pituitary-surgery setting has been evaluated in only a few studies. A multicentre study, 50 out of 205 patients who developed CDI revealed that a copeptin level of <2.5 pmol/L is accurate in establishing the diagnosis of CDI with a specificity of 97% and positive predictive value of 81% when measured within 24 hours of surgery.[52] In contrast, a value of >30 pmol/L almost excluded the diagnosis with a negative predictive value

Table 1: Biochemical parameters in patients with post-operative diabetes insipidus

Parameter	Description
Fluid balance	Variable, usually negative (more output than input)
Urine output	At least >2 mL/kg/h for two consecutive hours in addition to other parameters
Serum osmolality	Normal, if the patient has free access to water, or high, >300 mOsmol/kg, if the patient has limited access to water
Serum sodium	Normal, if the patient has free access to water, or high, >145 mmol/L, if the patient has limited access to water
Urine osmolality	Persistently <300 mOsmol/L
Urine specific gravity	Persistently <1.005
Copeptin	<2.5 pmol/L

Table 2: General management strategies for a patient with diabetes insipidus

Immediate postoperative period
• Assessment of volume and hydration status; measurement of serum sodium
• Close monitoring of serum sodium and urine output
• Optimisation of fluid replacement
• Consideration of desmopressin therapy in a patient with excessive and inappropriately dilute urine output
• Titration of desmopressin dose to keep 24-hour urine output above the normal range (15–30 mL/kg/day)
After hospital discharge
• Limiting fluid intake to the amounts required to satisfy thirst
• Performing electrolyte panel checks in any unwell patient after hospital discharge; close postoperative follow-up
• Monitoring for water intoxication and hyponatremia
• Delaying a dose of desmopressin once or twice per week to allow an aquaresis to occur
• Regular counselling of patient and their family about the principle of the treatment regime

Table 3: Management of hypodipsia/adipsia with central diabetes insipidus

• Set a target (kg) at the weight the patient is known to be euvolemic and normonatremic
• Fix 24-hour urine output at 1.5–2 L
• Determine the obligate fluid intake (approximately 1.5 L)
• Measure weight daily
• Daily water intake = obligate volume + (target weight – daily weight)
• Check plasma sodium weekly
• Educate patients and their family about the principle of the treatment regime

(NPV) of 95%. The performance of the test was better when performed <12 hours after surgery with lower accuracy beyond 24 hours. Similarly, the test proved superior in predicting persistent rather than transient DI (68% versus 32%). Another study of eight out of 58 patients with CDI with a standardised copeptin testing time showed that a peak copeptin level of <12.8 pmol/l at 60 minutes post-extubation predicted CDI, while permanent CDI was excluded with 100% NPV in those with a level of >4.2 pmol/L.[53] Interestingly, there was no significant difference in the copeptin level between the two groups in the subsequent post-extubation assessments at 6–48 hours.

Copeptin is a promising marker that will likely be a routine diagnostic test in the evaluation of CDI in the future. However, presently, the limited number of studies about copeptin use, the uncertainty about the optimal time of its measurement after surgery and the limited availability of the assay are factors limiting its widespread use. Table 1 summarises the various parameters that are frequently needed to be evaluated in post-pituitary-surgery patients and the expected changes in these parameters in patients with postoperative DI. A risk-based algorithm is proposed on the frequency of laboratory investigation to identify DI in the postoperative period [Figure 1].

TREATMENT

Although ADH secretion impairment and the disturbance of fluid balance often begin during the intraoperative period, CDI usually presents within a few hours after surgery. It is imperative to rule out intraoperative fluid overload and glycosuria as potential causes of polyuria. It is also noteworthy that patients with acromegaly may experience increased urinary output following the resection of their pituitary mass due to diuresis of excess fluid within the soft tissues.[54,55] Furthermore, approximately 50% and 80% of patients with transient DI recover within seven and 90 days of surgery, respectively.[56] As such, patients are advised to monitor for the cessation of thirst sensation and resolution of polyuria as potential signs of DI recovery. Moreover, periodic monitoring of electrolytes can be useful to confirm DI recovery, as water deprivation tests are not routinely recommended in this situation.[57] An additional advice is to delay desmopressin (DDAVP) dose for a few hours to see if increased thirst and polyuria persist.[57]

Patients require continuous monitoring of fluid intake and urine output and frequent assessment of electrolyte. DDAVP should be used cautiously as required, especially during the first two weeks postoperatively to avoid hyponatremia due to over-replacement.[31] Treatment of postoperative CDI is multifaceted and can be divided into acute or chronic phases, depending on the stage of the disease, to restore osmotic equilibrium. Although specific guidelines related to the management of postoperative DI are unavailable, in the recent past, a disease state review, followed by guidelines on hypopituitarism, was published, offering some guidance to the clinical management.[42,58] The general strategies of management of CDI are presented in Table 2. The acute phase management covers the first two phases of the triphasic water dysregulation phenomenon.

Acute Management of Central Diabetes Insipidus

FREE WATER ACCESS

The management is straightforward, provided there is an intact thirst mechanism, i.e. the patient is not receiving fluids for any reason and can drink water at will. Water balance can be achieved under such a situation as long as the patient can consume enough fluids.[59,60] Patients with a decreased level of consciousness and impaired thirst mechanisms or those on intravenous (IV) fluids will require continuous adjustment of IV fluids and pharmacotherapy to maintain adequate hydration and sodium equilibrium. The appearance of hypernatremia and polyuria along with dehydration heralds the onset of CDI. It should be aggressively sought out during the immediate postoperative period as hypernatremia can cause brain shrinkage, leading to vascular rupture and intracranial bleeding, along with other complications.[61]

The serum sodium level can be normalised safely at a correction rate of 1 mEq/L/h without any untoward complications.[62,63] Hypotonic fluids should be used when intravenous fluids are mandated. The least amount of fluid possible should be used and rapid overcorrection must be avoided as it can lead to cerebral edema.[63]

VASOPRESSIN

Vasopressin is available as an aqueous solution. Due to its short half-life of around 20 minutes, it should be administered through IV infusion when acute control of antidiuresis is needed.[64] Infusion is usually started at a rate of 0.25–1.0 micro unit/kg/h and titrated every half hour after that to maintain the urine output rate at around 100 mL/h and/or urine specific gravity at around 1.010–1.020.

DESMOPRESSIN

DDAVP (1-deamino-8-D-arginine vasopressin) is a synthetic analogue of vasopressin, having a prolonged action profile with minimal vasopressor activity. It can be administered orally, intranasally, subcutaneously or intravenously.[65] Studies have shown a definite relationship between the magnitude and duration of its therapeutic effect and its IV dosage. In patients with CDI, 1 μg IV 'push' infusion can increase urine osmolality to a maximum of 700–800 mOsmol/kg.[66,67] Further increase in dose, from 1 to 8 μg led to prolongation of the duration of action from around 26 hours to 46 hours. The magnitude and duration of its therapeutic effects showed large interindividual variability attributed to individual differences in renal concentration abilities, as it persisted even when the dose was increased to more than 2 μg.[67–70]

Further studies have shown that the antidiuretic efficacy depends on the total dose as well as the rate of increase in plasma DDAVP level.[71] The human kidney loses concentrating capacity in the absence of vasopressin. Therefore, once treatment is initiated, it requires at least eight hours of continued therapy for full recovery.[72] According to several studies, the parenteral DDAVP can be administered safely to acutely ill patients with CDI. However, the needed dose depends on the individual response, intactness of thirst mechanism and other factors determining fluid intake. In patients with intact thirst mechanisms, a starting dose of 0.25–0.50 μg twice daily as an IV infusion over two hours is usually administered, which is adjusted further to normalise urine output and maintain sodium equilibrium. A smaller dose of 0.06–0.125 μg is usually preferred with further titration to the desired effects for patients who are unable to drink at will or are on IV fluids. Although hyponatremia can be a manifestation of excessive DDAVP administration, the second phase of the triphasic water dysregulation phenomenon also presents with hyponatremia. Both of these have the same underlying mechanism and management principles that require withholding DDAVP along with careful electrolyte and fluid balance monitoring.

CHRONIC MANAGEMENT OF CENTRAL DIABETES INSIPIDUS

Since CDI rarely remits once established, it requires continuous, complete and around-the-clock management of the polyuria and maintenance of sodium and water equilibrium. Hypernatremia rarely goes unnoticed as it is always associated with polyuria and dehydration. Management principles of hypernatremia are same as mentioned above; however, in case the duration of hypernatremia cannot be ascertained, the serum sodium level should be corrected at a rate of 0.5 mEq/L/h, with no more than an 8–10 mEq/L decrease over 24 hours, while keeping the target sodium level at 145 mEq/L.[61,63,73]

Minimising the risk of hyponatremia due to excessive water retention is another critical challenge as it can be occasionally symptomatic and, rarely, life-threatening. Excessive fluid consumption suppresses vasopressin secretion in normal subjects by non-osmotic mechanisms, leading to diuresis and thus preventing over-hydration.[74,75] This 'escape' mechanism is not possible in patients with CDI as they are on exogenous long-acting desmopressin. Consequently, dilutional hyponatremia occurs. A longer-acting form of antidiuretic therapy and limiting fluid intake to the amounts required to satisfy thirst are the possible ways to achieve this goal. Titration of antidiuretic dose to keep 24 hours urine output within the normal range (15–30 mL/kg/day) is equally important.[76]

DESMOPRESSIN – NASAL SPRAY

Intranasal DDAVP has an absorption ratio of around 10–20% when compared to IV preparation in patients with CDI.[77] Moreover, it has interindividual and intraindividual variability in the magnitude and duration of its antidiuretic effect. The variability is irrespective of age, severity of polyuria or body-weight,[78,79] leading to the duration of action ranging from 4–18 hours to 8–24 hours seen with 5–10 and 20 μg, respectively.[69,80,81] The intranasal preparation is useful as it allows individualisation of treatment and dose titration by metered-dose spray (2.5–10 μg per spray). One must note that the absorption of nasal DDAVP may be decreased in the setting of nasal inflammation and rhinorrhoea, such as in upper respiratory tract infections, and therefore patients may need to use extra doses or shift to other routes if polyuria and dehydration are present.

DESMOPRESSIN ORAL TABLETS

Due to their large molecular size and susceptibility to enzymatic degradation coupled with short plasma half-life, vasopressin and DDAVP were initially considered to be unsuitable for oral use. However, despite low oral bioavailability of around 16%,[82] a stable antidiuretic effect with a clear dose–response relationship has been observed in clinical trials,[83] and preparation strengths (0.1, 0.2 and 0.4 mg) are available for oral use. DDAVP oral doses required for equivalent antidiuretic efficacy are around 10–20 times of the intranasal doses; however, the ease of administration makes oral formulations the preferred route of treatment for most patients. Although individualisation of therapy and titration of the dose is needed, 0.1–0.2 mg every eight hours is the usual maintenance dose,[80] while less frequent dosing, such as once or twice daily, is generally sufficient for infants and children.[84]

Desmopressin Oral Formulations – Oral Melt

Since 2005, DDAVP has been available as a sublingual lyophilizate (Melt) formulation containing 60, 120 and 240 µg, having bioavailability of around 25%.[85] In a recent study, DDAVP Melt has shown a similar level of antidiuretic control and was found to be as efficacious as intranasal DDAVP in both children and adults.[86]

Central Diabetes Insipidus in Specific Populations

Neonatal Infants/Children

The treatment of CDI in this group requires consideration of their diets which contain a proportionally larger amount of water. Therefore, to prevent hyponatremia, urine volume must not be reduced too much and careful dose titration with close input/output and plasma sodium monitoring are required. Continuous intravenous infusion of low dose DDAVP (0.1–0.2 µg s.c./i.m) or arginine ADH (0.25–3 mU/kg/h) under intensive monitoring is often used in the first 24–48 hours postoperatively.[87,88] Once CDI is stable and permanent, regular DDAVP can be prescribed. A diluted rhinyl preparation of nasal spray in the amount containing 1–5 µg of DDAVP once or twice daily usually provides good control of CDI in infants.[89] DDAVP can be administered subcutaneously in doses ranging from 0.02 to 0.08 µg once or twice daily.[90] Children and their parents need to be educated about the features of water intoxication and the hazards of excessive fluid intake.

Pregnancy and Lactation

DDAVP, being resistant to placental leucine aminopeptidase, can be administered safely to pregnant women, both for gestational DI as well as to patients with pre-existing CDI who become pregnant.[91,92] Compared to non-pregnant women, the doses needed are usually the same or slightly higher. Placental leucine aminopeptidase usually disappears in 4–6 postpartum weeks when DDAVP can be discontinued in patients with gestational DI. It should be kept in mind during the monitoring of therapeutic effects that serum sodium level during pregnancy decreases typically by approximately 5 mmol/L compared to the nongravid state. As DDAVP appears in an infinitesimal amount in breast milk, it can be continued during lactation.[93]

Elderly

As mentioned above, CDI requires lifelong management and, even if the underlying cause is eliminated, CDI once established rarely remits. The treatment of CDI in the elderly does not differ much from that in young adults, though the former faces a higher risk of developing hyponatremia, primarily when intranasal DDAVP is used.[78] The aetiology is not clear at present. Abnormalities of osmoregulation of thirst and fluid intake, along with increased renal sensitivity to DDAVP, may be the possible explanation as this population is known to be affected by these factors.[94]

Hypodipsia/Adipsia with Central Diabetes Insipidus

Anterior hypothalamus injury leading to osmoreceptor damage culminates in the absence or deficiency of thirst and results in the rare occurrence of adipsic DI. As a result, these patients have neither of the homeostatic mechanisms required for water balance regulation. Consequently, their management becomes difficult and they suffer from wide fluctuation in serum sodium levels.[95] In addition, during acute illnesses, patients can develop life-threatening hypernatremia, resulting in somnolence, seizures, hemiplegia, coma and acute renal failure and can experience thrombotic episodes. Furthermore, other complications such as obesity and sleep apnoea, which is largely attributed to hypothalamic abnormalities, may be seen in association with adipsic DI; these conditions contribute to the excess morbidity and mortality found in a patient with adipsic DI.[96] It becomes necessary to prescribe fluid intake on a sliding scale based on daily weight and serum sodium level.[97] DDAVP, alone or in combination with hydrochlorothiazide, is a useful agent in this regard.

An alternative and more practical approach is to set a target weight (kg) at which the patient is known to be euvolemic and normonatremic and maintain fixed urine output at 1.5–2 L with a fixed amount of DDAVP. Furthermore, daily fluid intake can be titrated as obligate load (1.5 L in temperate climates) + (target weight – daily weight) to maintain volume status, sodium and osmolality within the defined range.[98] Successful treatment can be achieved through daily measurement of body weight and perhaps weekly serum sodium measurement along with careful monitoring and patient and family education.[98] Additionally, due to the high rates of venous thrombosis and thromboembolism in patients with adipsic DI, giving low-molecular-weight heparin during periods of hypernatremia dehydration is recommended. Furthermore, screening for sleep abnormalities is indicated.[99] The principles of management of adipsic DI are displayed in Table 3.

Conclusion

CDI is a frequent complication that occurs in patients who undergo surgery for pituitary and suprasellar tumours and is the commonest leading cause for hospital readmission of these patients. Therefore, clinicians dealing with these patients need to perform a thorough preoperative risk assessment in order to identify known predictive factors for CDI, such as in patients with craniopharyngioma and with larger tumours, in order to have clear strategies in place for early diagnosis and management. Moreover, postoperative evaluation should be performed in the early and late postoperative periods in order to reduce the risk of complications and unnecessary readmissions to the hospital. While the management of CDI which complicates surgery for pituitary and suprasellar tumours is a commonly encountered topic, it nonetheless remains a challenging area for clinicians and requires high standards of medical knowledge in tandem with superior clinical experience and skills, especially regarding the decision about when to start desmopressin therapy and for how long, as well as planning the long-term follow-up for those who develop permanent CDI.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHORS' CONTRIBUTION

MHA contributed to study design. All authors contributed to the literature review and data collection. All authors drafted the initial manuscript. MHA, MMA, and IB edited the manuscript. MA, KMD, MM and SAB made critical revision and approved final version. All authors reviewed and approved the final version of the manuscript.

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