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Diabetes Insipidus and the use of desmopressin in hospitalised children

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Abstract:

There have been recent concerns raised about the hospital care of patients with diabetes insipidus and the morbidity and mortality associated with delay or omission of administration of desmopressin. This is a review of diabetes insipidus and desmopressin with a practical guide to management of these complex patients for the general paediatrician or intensive care physician caring for these children out of hours when access to specialist endocrinology may not be available.

Introduction

In February this year NHS England released a patient safety alert highlighting the associated mortality and morbidity when desmopressin is omitted in individuals with cranial diabetes insipidus [1]. Over a seven-year period the UK National Reporting and Learning System had identified 76 near misses, 56 dosing errors leading to harm and four cases where desmopressin omission has resulted in severe dehydration and death [1]. Gleeson *et al*, concerned about the care of adult patients with diabetes insipidus (DI) when admitted to hospital, recently reported a retrospective audit in which desmopressin was missed or delayed in 88% of admissions, in two thirds of cases because medication was unavailable [2]. Both publications raise awareness of the risks and call for improved education, easier access to desmopressin in the inpatient setting and heightened pharmacovigilance; using increasingly popular e-prescribing to flag patients on desmopressin and alert endocrinologists to their admission [1, 2].

To our knowledge there are no comparable data available in paediatrics, but the risks of children with DI not receiving the care they require is a concern. Paediatricians increasingly face complex children, on multiple, often unfamiliar, drugs, requiring management from generalists or intensivists when admitted out of hours who may not have immediate access to specialist paediatric endocrinology. To compound the issue paediatric staff are often familiar with the more common indication for desmopressin, enuresis, and therefore may not identify it as a critical medication, increasing the risk of omission. These patients are often on concomitant glucocorticoid replacement, which may complicate matters further.

It is therefore timely to review situations when the generalist or intensivist may come into contact with patients with DI and to summarise management strategies and pitfalls to avoid.

What is Diabetes Insipidus?

Diabetes insipidus (DI) describes polyuria and polydipsia occurring due to an inability to concentrate urine. Central or cranial DI occurs when there is a lack of arginine vasopressin (AVP) (interchangeably referred to as anti-diuretic hormone (ADH), vasopressin or argipressin) and nephrogenic DI when the kidneys fail to respond to the AVP secreted by the

posterior pituitary gland. AVP acts on receptors located in the collecting duct of the kidney, enabling aquaporin channels to allow water reabsorption from the duct lumen into the cells. DI is rare, with an estimated prevalence of 1 in 25,000 [3]. In children cranial DI is the cause in more than 90% cases [4]. There are many causes from abnormalities of development to acquired forms (table 1). Children with other pituitary hormone deficiencies, those who have had intracranial tumours (in particular craniopharyngiomas) and pituitary surgery, are at particular risk.

Children with DI may exhibit unusual behaviours (e.g. licking condensation from windows, drinking from animal water bowls) to access fluid and are not generally fussy about the source or the flavour of the liquid. This can help in distinguishing DI from habitual drinking, where flavoured drinks are often preferred. The reduction in AVP results in polyuria (urine output >2 L/m^2/day) (table 2) in the absence of alternative solute diuresis e.g. calcium and glucose [3]. This may present as new-onset enuresis in older children with a commensurate rise in serum sodium and plasma osmolality, leading to osmoreceptor activation and a compensatory polydipsia. When children have access to fluids, serum sodium can be kept within 2% of normal levels [5].

The diagnosis of DI can be challenging and distinguishing from other causes, most notably habitual drinking in children, difficult. A high serum osmolality (>300 mOsm/kg) in the presence of inappropriately dilute urine (<300 mOsm/kg or urine/plasma osmolality ratio <1) from paired early morning samples is diagnostic. Hypernatraemia (sodium >145 mmol/l) may or may not be present. However, in many cases of DI there is a partial release of AVP during periods of dehydration, thus a water deprivation test, carried out in a specialist centre, may be required to reach a definitive diagnosis. The initial diagnosis, differentiation and subsequent out-patient management of DI, particularly infants, has been covered comprehensively elsewhere [3-6].

Desmopressin

Mild or transient forms of DI may be managed with unrestricted access to water but in the majority desmopressin (*1-desamino-8-D-arginine vasopressin* - DDAVP), a synthetic AVP analogue with prolonged duration of action, is prescribed. Desmopressin reduces urine

output by binding to the G protein-coupled V2 receptors predominantly found in the collecting duct. Binding results in activation of the aquaporin channels by adenylate cyclase increasing cAMP-dependent protein kinase and causing translocation of preformed aquaporin channels to the apical membrane, significantly increasing water permeability and thus osmotic reabsorption of free water [7].

When desmopressin is given intranasally or orally, maximum plasma concentrations are reached in 40-55 minutes, with a half-life of 3-4 hours [8]. A patient's response to desmopressin is idiosyncratic with sensitivity varying between individuals and dependent on the underlying pathology and amount of residual or functional posterior pituitary tissue in patients with cranial DI. The dosing is therefore based on symptom control rather than age or size. Doses should be started low and increased to allow normal drinking and full nights sleep whilst avoiding hyponatraemia with excessive antidiuretic effects. Desmopressin is usually administered orally or nasally but sublingual, subcutaneous, intramuscular and intravenous formulations exist. Generally the oral route is preferred for the management of DI in children, the nasal route being preferred in adults and should be avoided when there are concerns about the integrity of the nasal mucosa e.g. allergic rhinitis or after transphenoidal surgery. Young patients requiring small doses may not be suitable for the nasal spray, which cannot deliver less than 0.1ml (10 micrograms). It is important to note that the formulations are not easily interchangeable, with exact information as to the relative bioavailabilities hard to come by [9]. An approximate conversion guide for children aged 12 and above, derived from multiple sources, is provided in table 3. There is significant variation in published bioavailabilities, particularly for oral and nasal formulations, and therefore these are not routinely used in clinical practice. Clinical monitoring of effect and dose adjustment is essential for children of all ages and we suggest early involvement of a paediatric pharmacist. Intravenous desmopressin (aqueous pitressin) is usually reserved for the paediatric intensive care setting where its very short half-life allows for greater flexibility in fluid management. Historically cranial DI has been treated with chlorpropamide, carbamazepine and clofibrate but synthetic AVP has now rendered the use of these outdated [10, 11].

In-patient management of a child with diabetes insipidus

Fluid management

Untreated DI carries a significant risk of dehydration by uncontrolled polyuria without adequate rehydration. In patients with well-established DI, polyuria is followed closely by polydipsia in an attempt to normalise intravascular pressure and hypernatraemia. This occurs as a result of osmoreceptor and baroreceptor activation. The primary aim of initial management of a patient with DI is to ensure they remain in a euvolaemic state, with a sodium at 135-150 mmol/l and a serum osmolality within normal limits. Patients with DI who have an intact thirst mechanism and who are able to tolerate oral fluid should have unrestricted access to fluids and should never be fluid restricted. However they should be encouraged only to drink enough to satisfy thirst, as excess fluid intake cannot be readily excreted. Electrolyte solutions are effective oral fluids in DI but if children refuse these they should be given any fluid they can tolerate. For patients who are unable to tolerate oral fluids or who are vomiting, fluid resuscitation and subsequent volume replacement is required to prevent hypernatraemia.

Fluid replacement will vary but in all presentations accurate fluid balance and judicious recording is the key to successful management. Particular care must be taken when transferring patients between wards or departments e.g. theatre to the ward, where fluid charts may differ. In the calculation of output insensible losses over a 24-hour period (300ml/m^2/day) must be included in the calculation. In infants or children who are not toilet trained, daily urine output can be estimated by weighing diapers before and immediately after each change. Intravenous fluid replacement is normally given as 0.9% saline to prevent a rapid reduction in serum sodium. If the sodium does not fall appropriately (0.5-1 mmol/hr), then 0.45% saline can be used instead. Calculating and matching fluid balance should occur at 6 hourly intervals and achieved by the following: Fluid input = urine output (+ other losses e.g. stoma) + 300mls/m^2/day of insensible loss.

Desmopressin

Desmopressin should be prescribed according to the patient's normal prescription unless they are unable to tolerate oral preparations. It is important to note that doses outside the recommended dose range may be required to treat DI in children. For patients requiring parenteral therapy intramuscular (IM) desmopressin is normally chosen, although

intravenous pitressin infusion can be used. By this route, daily, and occasionally twice daily, doses of IM desmopressin are required to safely manage DI until the patient is able to tolerate oral fluids and medication. Following the first dose of IM desmopressin a dilute polyuria should be observed before a subsequent dose is administered to prevent fluid retention and hyponatraemia. Conversely, a second IM dose may be required after 12 hours if the patient's urine output has not adequately reduced.

Monitoring

Urine output in patients with established DI will normally indicate over or under treatment with desmopressin. Older children will also continue to report thirst. Daily urine outputs and urine osmolality can be used to guide management (table 4). In patients who are catheterised, urine output should be measured on an hourly basis (preceding hour to current hour), allowing rapid changes to be detected. Where patients can pass urine freely, urine output should be calculated in 4-6 hour blocks. Averaging urine output over a 24-hour period, or from a set baseline to the point of measurement, may result in a delay identifying polyuria. In unwell patients with DI regular monitoring should include a minimum of four hourly measurements of serum electrolytes, with paired serum and urine osmolality.

Although a crude measurement of urine osmolality, specific gravity (SG) provides a rapid estimate of urine concentration. The urine is considered dilute if SG <1.005. Specific gravity can approximate osmolality by multiplying the last two digits by 40. For example urine SG of 1.005 = osmolality of 05 X 40 = 200 mOsm/Kg, SG 1015 = 15 x 40 = 600 mOsm/Kg. Daily patient weight will also indicate fluid loss or retention in the preceding 24 hours.

Special considerations

Concomitant administration with hydrocortisone

It is important to ascertain whether a patient on desmopressin is also on steroid replacement medication [2]. Cortisol is required for the excretion of free water. Cortisol insufficiency can therefore lead to hyponatraemia, which will be exacerbated by the administration of desmopressin. Children with pituitary dysfunction are often taking hydrocortisone and desmopressin concomitantly, and when unwell, hydrocortisone should be increased to match

endogenous cortisol requirement. Unwell children with anterior and posterior pituitary dysfunction should increase their dose of hydrocortisone and have serum electrolytes checked before further administration of desmopressin to prevent dilutional hyponatraemia [12]. Children should be allowed to drink freely, as the thirst stimulus will serve to regulate serum sodium whilst off desmopressin. In addition, when steroids have been increased ensure that the subsequent diuresis is not secondary to hyperglycaemia.

Overdose with desmopressin

Overdose with desmopressin in patients with DI is rare, and should be managed by a specialist. Symptomatic dilutional hyponatremia is the main complication but in rare cases, cerebral oedema may result from intravascular fluid shifts. No further desmopressin should be given. If investigations indicate hyponatraemia with low serum osmolality paired with high urine osmolality and oliguria, then this is one of the only circumstances where fluid restriction may be necessary. In severe hyponatraemia hypertonic saline infusion may be required to carefully normalise serum sodium.

Adipsic DI

Patients with complex midline CNS abnormalities may have defective AVP osmoregulation leading to low or no thirst response to plasma hypertonicity. Up to 20% of patients following pituitary surgery are reported to have thirst dysregulation [13, 14]. Fluid management in the adipsic DI patient is challenging. Monitoring admitted patients with established adipsic DI should follow exactly the same process as those with an intact thirst mechanism but personalised fixed fluid regimes are required to ensure they receive the appropriate volume of fluid in relation to their dose of desmopressin.

Summary

Whilst the initial management of patients with established DI outside specialist centres may appear both daunting and challenging, adhering to simple key principles will ensure the

patient remains safe. Ensure that all staff are aware that the patient has DI and understand that strict fluid monitoring and management will ensure stability. Patients with DI should never be fluid restricted, desmopressin should not be omitted or delayed (other than when glucocorticoid doses have been increased) and patients should not self-administer desmopressin. Desmopressin should also be regularly available out of hours to avoid administration delays. A paediatric endocrinologist should be contacted as soon as possible after admission. Given the potential risk of morbidity and mortality as a result of failure to adhere to simple principles, in particular with out of hours and unplanned admissions, we recommend that a hospital alert system for patients with DI is established in line with the recommendations from NHS England [1, 2].

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Key messages (textbox):

- Never fluid restrict a patient with diabetes insipidus.
- Desmopressin doses are highly individual and should be monitored by clinical effect.
- The doses of the different formulations of desmopressin are not interchangeable. Traditionally a "rule of 10s" conversion has been used but the bioavailabilities do not support this and we recommend seeking pharmacy or endocrine advice when converting a patient on desmopressin to a different formulation.
- Strict fluid balance, and regular serum electrolyte, osmolality and urine osmolality monitoring are needed to ensure safe inpatient care of patients with DI.

References

1. Patient Safety Alert. NHS/PSA/W/2016/001. February 2016.

2. Gleeson, H., Bonfield, A., Hackett, E., Crasto, W. Concerns about the safety of patients with diabetes insipidus admitted to hospital. Letter to the Editor. Clinical Endocrinology (2016), 84, 946-951.
3. Di Iorgi N, Napoli F, Allegri AE, et al. Diabetes insipidus – diagnosis and management. Horm Res Paediatr. 2012;77(2):69-84.
4. Dabrowski E, Kadakia R, Zimmerman D. Diabetes Insipidus in infants and children. Best Pract Res Clin Endocrinol Metab. 2016;30(2):317-328.
5. Robertson G. Diabetes insipidus - differential diagnosis and management. Best Pract Res Clin Endocrinol Metab. 2016;30(2):205-18
6. Rivkees SA, Dunbar N, Wilson TA. The management of central diabetes insipidus in infancy: desmopressin, low renal solute load formula, thiazide diuretics. J Pediatr Endocrinol Metab 2007;20:459-69.
7. Oiso Y, Robertson GL, Norgaard JP, et al. Treatment of neurohypophyseal diabetes insipidus. Journal of Clinical Endocrinology and Metabolism 2013; 98 (10); 3958-3967.
8. Richardson DW, Robinson AG. Desmopressin. Ann Intern Med 1985;103:228-39.
9. Ferring Pharmaceuticals Ltd. DDAVP (tablets, melts, nasal spray). Summary of Product Characteristics July 2012. http://www.medicines.org.uk.
10. Thompson P, Earll JM, Schaaf, M. Comparison of clofibrate and chlorpropamide in vasopressin-responsive diabetes insipidus. Metabolism, 1977. 26 (7): 749-762.
11. Stephens WP, Coe JY, Baylis PH. Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. British Medical Journal, 1978; 1: 1445-1447.
12. Elder CJ, Dimitri P. Hydrocortisone for adrenal insufficiency. Arch Dis Child Educ Pract Ed. 2015;100(5):272-6
13. Smith D, McKenna K, Moore K, et al. Baroregulation of vasopressin release in adipsic diabetes insipidus. J Clin Endocrinol Metab 2002;87:4564-8.
14. Smith D, Finucane F, Phillips J, et al. Abnormal regulation of thirst and vasopressin secretion following surgery for craniopharyngioma. Clin Endocrinol (Oxf) 2004;61:273-9.

Table 1. Causes of Diabetes Insipidus

	Central DI	Nephrogenic DI
Genetic	Autosomal dominant (AVP-NP11) Autosomal recessive (AVP-NP11) Wolfram Syndrome (WFS	Autosomal dominant (aquaporin-2) Autosomal recessive (aquaporin-2) X-linked recessive (AVP-V_2 receptor)
Congenital	Septo-optic dysplasia Pituitary agenesis/hypoplasia Holoprosencephaly Infections e.g. CMV	
Acquired	Intracranial tumours e.g. craniopharyngioma Intracranial infections e.g. meningitis Intracranial infilitration e.g. Langerhan's cell histiocytosis Autoimmune hypophysitis Head trauma Cranial hypoxic-ischaemic injury Intracranial surgery Idiopathic	Iatrogenic – lithium, chemotherapeutic agents Metabolic e.g. hypokalaemia, hypercalcaemia Renal outflow obstruction Renal hypoxic-ischaemic injury Chronic kidney disease

Table 2. Definitions of polyuria at different ages

Age	Urine output defining polyuria
Birth	150 ml/kg/24 hr (>6 ml/kg/hr)
Until 2 years	100-110 ml/kg/24 hr (>4 ml/kg/hr)
Older child/adult	40-50 ml/kg/24 h (>2ml/kg/hr)

Table 3. Approximate conversion factors for different routes of administration of desmopressin for children aged 12 years and above. [9].

Route of administration	Usual dose range for treatment of DI (micrograms/day)	Approximate bioavailability (%)	Suggested conversion factor for daily dose*
Intravenous/ Subcutaneous	**1-4**	**100**	**1**
Intranasal	**10-40**	**10**	**10**
Oral	**200-1200**	**0.5**	**200-300**
Sublingual	**120-720**	**0.83**	**120-180**

*** These conversions are an approximate guide only, bioavailability varies and responses to desmopressin are individual therefore dose should be altered based on clinical parameters.**

Table 4. Monitoring adequacy of desmopressin dose in hospitalised patients with DI

Clinical scenario	Urine output	Urine osmolality
Ideal	20-30 ml/kg/day	400-800 mOsms/l
Desmopressin omitted/dose inadequate	> 4ml/kg/hr	<100 mOsms/l)
Excess desmopressin administered	< 1 ml/kg/hr	>1000 mOsms/l