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Case report

Severe water intoxication secondary to the concomitant intake of non-steroidal anti-inflammatory drugs and desmopressin: a case report and review of the literature

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ABSTRACT

Most of the clinical data on the safety profile of desmopressin (DDAVP), which is an effective treatment for both polyuric conditions and bleeding disorders, originate from studies on the tailoring of drug treatment, whereas few reports exist describing severe side effects secondary to drug-drug interaction. We herein describe a case of severe hyponatremia complicated by seizure and coma due to the intake of non-steroidal anti-inflammatory drugs (NSAIDs) in a patient on DDAVP replacement therapy for central diabetes insipidus (DI). A 50-yr-old Caucasian man, with congenital central DI, developed an episode of generalized tonic-clonic seizure, resulting in coma immediately after being admitted to the Emergency Unit for weakness and emesis. Based on his medical history and clinical findings, water intoxication secondary to ketoprofen intake (200 mg/day for the last 3 days) concomitant with DDAVP replacement therapy (Minirin® 60 mcg 4 tablets a day) was hypothesized as being the cause of the severe euvolemic hypotonic hyponatremia (natremia 113 mEq/l, plasma osmolality 238 mOsm/Kg). After standard emergency procedures, appropriate gradual restoration of serum sodium levels to the normal range was achieved in 72 hours. Hydratation was maintained according to water excretion and desmopressin therapy was re-introduced. We discuss this case report in the context of the published literature. The present report first highlights the potentially life-threatening side effects associated with over-the-counter NSAIDs during DDAVP replacement therapy for central DI. Risks and benefits of co-treatment should be carefully considered and therapeutic alternatives to NSAIDs should be recommended to patients with central DI in order to improve DDAVP safety.

Key words: Central diabetes insipidus, DDAVP, Hyponatremia, NSAIDs, Seizure, Water intoxication

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INTRODUCTION

Numerous clinical trials have validated the efficacy and tolerability of desmopressin diacetate arginine vasopressin (DDAVP), a synthetic analogue of vasopressin that is widely employed in both polyuric conditions including central diabetes insipidus, primary nocturnal enuresis and nocturia and bleeding disorders (e.g. von Willebrand's disease).[1] The individual tailoring of drug treatment has been particularly emphasized, since recent pharmacokinetics and pharmacodynamics studies have highlighted a considerable variability not only in regard to DDAVP formulation (intranasal, injectable or sublingual), but also in gender- and age-related drug response.[2-4] Moreover, several drugs, such as lithium and demeclocycline, are liable to impair the water reabsorption effect of desmopressin, while this effect may be potentiated by other drugs of widespread use, such as non-steroidal anti-inflammatory drugs (NSAIDs), triciclyc antidepressants, carbamazepine and loperamide.[5]

Data available in the literature on the adverse effects of DDAVP and co-administered drugs mostly derive from databases for adverse drug reaction or national drug registers that have elderly patients on DDAVP for nocturnal enuresis as the investigated population. Here we firstly describe a case of severe water intoxication complicated by seizure and coma secondary to concomitant intake of NSAIDs in a male adult patient suffering from congenital central diabetes insipidus treated with DDAVP for more than 40 years.

CASE REPORT

A 50-year-old man, referred in the past to our Endocrinology Unit for congenital diabetes insipidus, was admitted to the Emergency Unit of Ospedale S. Paolo complaining of worsening nausea, two episodes of emesis and progressive weakness over the past 12 hours, whilst he denied having fever or any other constitutional symptoms. Moreover, the patient reported no known allergies as well as no history of smoking, alcohol or recreational drug ingestion. Shortly after admission he developed an episode of generalized tonic-clonic seizure, resulting in coma.

Regarding his pharmacological history, the day before entry he took his standard dose of sublingual desmopressin (Minirin® 60 mcg 4 tablets a day) and ketoprofen (200 mg/day in the last 3 days) for cervical pain related to spondylosis. Overall reported fluid intake was about 1.5 L./day. The diagnostic workout performed at the time of diagnosis (i.e.: plasma sodium level 147 mEq/l, plasma osmolality of 297 mOsm/Kg, urinary volume of 66 ml/Kg/24 h) and a recent medical record, reporting a normal pituitary gland with absence of the physiological posterior bright signal at MRI of the sellar region, were in agreement for the diagnosis of complete central diabetes insipidus. Moreover, recent normal functioning of the anterior pituitary (normal basal and ACTH-stimulated cortisol secretion; normal PRL, total testosterone, IGF-I, TSH and free thyroid hormones levels) was reported. His medical history was otherwise unremarkable and no previous convulsive disorders were reported. The post-critic physical and neurological examination showed: unconscious psychomotor agitation (Glasgow Coma Scale score of 9), normal clino- and orthostatic blood pressure, heart rate and temperature (119/70 and 120/75 mmHg, 95 bpm, 36.4°C, respectively) and no respiratory distress (pO_2 105 mmHg, SpO_2 97%, pCO_2 26 mmHg) or other neurological alterations. Moreover, no clinical signs of volume expansion or depletion (i.e. subcutaneous edema or dry mucus membranes) were detectable. Hematological parameters at admission to the Intensive Care Unit revealed severe hyponatremia, metabolic lactic acidosis and rhabdomyolysis [Table 1]. On further work-up, urine toxicological screening, carbohydrate-deficient transferrin, basal cortisolemia and TSH levels, chest X-ray and brain CT scan were normal. Water intoxication secondary to desmopressin and NSAIDs co-administration, mimicking a syndrome of inappropriate antidiuretic hormone hypersecretion, was hypothesized as the possible cause of the severe euvolemic hypotonic hyponatremia observed at entry, while the acute fall in sodium levels was assumed responsible for the seizures and coma. Since other concomitant predisposing comorbidities (e.g. infections, diarrhea or fever), excessive fluid intake and DDAVP overdose were excluded, neither did the hypothesis of a possible contributing factor of nausea scarcely seem plausible; in fact, as mentioned above, it was improbable that a residual endogenous ADH was released in response to that stimulus, whilst the close temporal relationship between NSAID admin-

Table 1. Laboratory analysis on admission to the Emergency Unit

Parameters (units)	Patient	Normal range
pH	7.1	7.35-7.45
HCO_3^- (mmol/L)	19	22-26
BE	-10.2	
Na^+ (mEq/L)	113	135-145
K^+ (mEq/L)	3.6	3.5-5.0
Cl^- (mEq/L)	76	95-105
Ca^{++} (mmol/L)	0.99	1.13-1.32
Plasma osmolality (mOsm/Kg)	238	275-295
CPK (UI/L)	433	1-195
Glucose (mg/dl)	109	65-110
Creatinine (mg/dl)	0.72	(0.5-1.0)
Azotemia (mg/dl)	17	(15-50)

HCO_3^-: bicarbonate ions; BE: base excess; Na^+: sodium ions; K^+: potassium ions; Cl^-: chloride ions; Ca^{++}: ionized calcium; CPK: creatine phosphokinase.

istration and fluid imbalance were strongly suggestive of pathogenic connection.

After therapeutic emergency procedures (including intravenous injection of benzodiazepine, voluven, sodium bicarbonate and propofol together with invasive mechanical ventilation support), a first-line 3% saline infusion was administered for about 12 hours in order to ensure a prompt reversal of neurological symptoms and overcome the crisis, restoring sodium concentration to 120 mEq/l; afterwards, the resuscitator decided to continue hyponatremia treatment by administering the aquaretic tolvaptan (Samsca®, Otsuka Pharmaceutical Co. Ltd.) 7.5 mg and hydratation was maintained according to water excretion. At the same time, desmopressin substitution was withdrawn; during the course of hospitalization, once the cause of hyponatremia was eliminated and water diuresis emerged, desmopressin therapy was also gradually restarted as shown [Table 2], but the usual regimen (Minirin 60 mcg 4 tablets a day) was reached only on day 6. In parallel, the clinical condition progressively improved and the patient completely recovered 72 hours after admission, being discharged 10 days later.

DISCUSSION

The present study reports for the first time a case of severe hyponatremia complicated by seizure and coma secondary to concomitant intake of DDAVP and non-steroidal anti-inflammatory drugs in a male adult patient suffering from congenital central diabetes insipidus who had been on desmopressin treatment for over 40 years without previous adverse effects. Therefore, although water retention associated with NSAID treatment is probably insignificant in healthy individuals,[6] to the best of our knowledge, what makes this case report unique is the occurrence of serious side effects due to the properties of NSAIDs to increase the antidiuretic effect of DDAVP, administered to replace a congenital ADH deficiency in a male patient.

Multiple cases of DDAVP-induced hyponatremia have been reported in both adults and children to

Table 2. Modifications of the various parameters during the initial treatment and the follow-up. Tolvaptan (7.5 mg/day) was administered on day 1, after a first-line 3% saline infusion; DDAVP, that was withdrawn on admission to the Emergency Unit, was gradually restarted on day 3, and the usual regimen was reached on day 6

Parameters (units)	Admission Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Discharge	Normal range
Input (l/day)	8000	2500	2250	3000	7500	12000	9500	4000	4700	3200	-
Output (l/day)	9000	4500	3500	4000	7000	12800	10000	4400	3700	4700	-
Sodium levels (mEq/L)	113	120	127	135	138	142	141	138	138	137	135-145
Plasma osmolality (mOsm/kg)	238	260	282	286	288	294	290	287	285	284	275-295
24-h Urinary sodium output (mEq/24 hrs)	143	172	142	200	280	377	300	150	115	nd	
Potassium levels (mEq/l)	3.6	4.4	4.7	4.3	4.4	4.3	4.2	4.1	4.0	4.3	3.5-4.5
Creatinine (mg/dl)	0.72	0.69	-	-	0.75	-	0.81	-	-	0.85	0.5-1.0

date,[7-9] even though the overall incidence remains very rare. In fact, this side effect is reported in less than 1 out of 10,000 patients treated and is generally related to treatment of nocturnal enuresis and coagulopathies rather than replacement therapy in central diabetes insipidus.[1,5]

In addition, the importance of individualizing the therapeutic approach has been particularly emphasized in the literature, on the basis of recent pharmacokinetics and pharmacodynamics studies that have highlighted a significant variability not only in regard to DDAVP formulation (intranasal, injectable or sublingual), but also in gender- and age-related drug response.[2-4] In particular, most of the cases of desmopressin-induced hyponatremia have occurred so far in females, this being consistent with experimental data in animals that show increased V_2R mRNA expression in female rats when compared to males, resulting in a physiologically increased gender susceptibility to the adverse effects of desmopressin. In this context, with regard to the influence of age, several studies have highlighted that the adult and elderly population may be more prone to hyponatremia from DDAVP treatment. Rembratt and colleagues, for example, have demonstrated how age is the single best risk factor predictor of clinically significant hyponatremia in desmopressin treatment for nocturia, ahead of low sodium levels at baseline, thus suggesting that the predisposing factor is not age *per se* but one or more dysfunctions that occur more frequently in the elderly.[10]

Furthermore, more recently, as concerns patients in the age group above 50 yrs old, Vinter Juul and colleagues demonstrated an increased incidence of hyponatremia with increasing dose of desmopressin, with women having a fivefold higher risk than men. [3]

Moreover, it is well known that a large number of pharmacological agents can cause hyponatremia by increasing endogenous AVP release or renal activity, or by interfering with water/electrolyte imbalance. In particular, drugs of widespread use, e.g. lithium and demeclocycline, are able to impair and others, e.g. NSAIDs, triciclyc antidepressants, carbamazepine and loperamide, to potentiate the water reabsorption effect of desmopressin.[5]

Most of the evidence available in the literature on the adverse effects of DDAVP and co-administered drugs derive from databases for adverse drug reaction or national drug registers and have elderly patients on DDAVP for nocturnal enuresis as the investigated population. In this respect, Callréus and collaborators carried out a critical appraisal of the Danish and Swedish spontaneous reporting database for adverse drug reaction.[11] They found that in elderly patients treated with DDAVP from 1990 to 2004 for nicturia, 6 out of 15 cases of hyponatremia reported were associated with the concomitant medication with cyclooxygenase inhibitors (diclofenac, indomethacin, celecoxib, etoricoxib or low-dose acetylsalicylic acid). The concomitant administration of DDAVP and other potentially adversely interacting drugs is a frequent event, particularly in elderly patients. In fact, according to the Swedish Prescribed Drug Register, between 2000 and 2007 the vast majority of patients over 60 years of age on DDAVP treatment also received other drugs, these potentially interfering with desmopressin action, such as NSAIDs, carbamazepine and tryciclic antidepressants.[12] Lastly, reviewing post-marketing surveillance of the U.S. Food and Drug Administration (FDA), among a total of 61 cases of hyponatremic-related seizures associated to DDAVP, mostly indicated for nocturnal enuresis, more than half of these cases presented with at least one concomitant drug or disease predisposing to hyponatremia and/or seizure. Based on these reports, the FDA indicated that DDAVP treatment should be undertaken only with careful monitoring of serum sodium concentration (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125561.htm).

Contrary to the multiple cases of hyponatremia reported in patients on DDAVP treatment, in only a few cases have serious side effects due to DDAVP and NSAIDs interaction been reported in the literature to date [Table 3]. Two case reports described the occurrence of severe hyponatremia and seizures in three patients treated with DDAVP and NSAID, without mentioning the possible causal relationship between the two treatments. In particular, Francis and collaborators described the occurrence of hyponatremia and seizures in a 3-year-old child with a family history of hemophilia following treatment with DDAVP for a bleeding tonsil.[13] In this case, diclofenac

Table 3. Review of the literature

N.	Series	Journal & year	No. of cases of hyponatremia	Patient	Reason for DDAVP treatment	Concomitant medication
1	Francis	Acta Anaesthesiol Scand, 1999	1	3 yrs-old child	hemophilia	diclofenac
2	Shindel	Urology, 2002	2	89-yr-old and 80-yr-old women	nocturnal polyuria	rofecoxib, aspirin
3	Gomez Garcìa	Haemophilia, 2003	1	50-yr-old woman	hemophilia	ibuprofen
4	Callréus	Eur J Clin Pharmacol, 2005	6	>60 yrs old	nicturia	diclofenac, indomethacin, celecoxib, etoricoxib and acetylsalicylic acid

was administered rectally shortly after anesthesia to provide post-operative analgesia. Although not pointed out by the authors, it is conceivable to speculate that NSAID, together with an over resuscitation using hypotonic intravenous fluids, had contributed to the convulsions and respiratory arrest. Similarly, Shindel and collaborators described two cases of elderly women taking desmopressin for nocturnal polyuria who developed severe hyponatremia; in both patients, concomitant administration of NSAID, i.e. rofecoxib and aspirin, respectively, was mentioned and it is reasonable to hypothesize the contribution of these drugs to the pathogenesis of sodium imbalance.[14] Gomez García and collaborators first emphasized the unsafe and potentially life-threatening combination of DDAVP and NSAID based on a case of hyponatremic coma arising from a combined use of DDAVP and ibuprofen in a middle-aged woman suffering from von Willebrand's disease.[15]

As far as the mechanisms involved in NSAIDs and desmopressin interaction are concerned, further studies are certainly required to shed more light. Although the role of AVP and prostaglandins (in particular, prostaglandin E_2, PGE_2) in renal collecting ducts has long been known, it is now clear that vasopressin-independent pathways may also take part in modulating diuresis.[16,17] In the collecting duct, PGE_2 may exert opposing effects according to the selective stimulated E-prostanoid receptor (EP1, EP2, EP3 and EP4), thus potentially initiating a variety of intracellular signaling cascades.

Zelenina and colleagues have demonstrated that in animal models, PGE_2 alone does not have effects on water channel aquaporin-2 (AQP_2) phosphorylation, but reverses the AVP-mediated translocation of AQP_2 to the plasma membrane, hence antagonizing water permeability, most likely through EP1 and EP3 receptors activation, although other proteins involved in vesicle trafficking cannot be excluded. Moreover, the cyclooxygenase inhibitors (e.g. indomethacin and diclofenac) induce a striking shift of AQP_2 from the intracellular vesicles pool to the plasma membrane-enriched fraction,[18] resulting in an enhanced antidiuretic effect, and this observation could explain the common NSAIDs-associated adverse effect of water retention.[6] On the other hand, these results disagree with other studies, where PGE_2 markedly increased expression and phosphorylation of AQP_2 *in vivo* and *in vitro*, leading to a heightened epithelium water permeability and opening up a new therapeutic approach with selective E-prostanoid receptors agonist for nephrogenic diabetes insipidus.[19]

The observation that treatment with NSAIDs causes a significant decrease in AQP_2 expression but not in PGE_2 levels in normal and water-restricted rats has led to the hypothesis that the action of these drugs at AQP_2 levels may be mediated by additional unknown effects.[16]

Differences in tubular cell sensitivity to desmopressin have been advocated by Odeberg and colleagues to explain the putative PGE_2-mediated gender difference observed in the human model. Interestingly, if the pharmacokinetics of DDAVP was not influenced either by piroxicam pre-treatment or the sex of the subject, during the pharmacodynamic study, the more pronounced antidiuretic effect observed in the

female may instead have been significantly reduced by piroxicam pre-treatment.[20]

In our case report, a potential weakness of our explanatory analysis was the lack of previous similar episodes of hyponatremia in a patient who has been treated with DDAVP for several decades. Since other predisposing factors (such as undercurrent systemic comorbidities or drug abuse) were excluded and it is highly unlikely that he had used NSAID before, it is plausible to assume that the detrimental interaction between NSAID and DDAVP was aggravated by a more pronounced sensitivity to desmopressin related to age.

Although management of hyponatremia is beyond the scope of this topic, it should be mentioned that the diagnosis and therapy of water intoxication can be challenging in critically ill patients. In fact, the clinical setting is often subtle or nonspecific and is mainly related to the degree of hyponatremia and to the swiftness of decrease in plasma sodium concentration. Moreover, since its delayed recognition or inappropriate treatment may lead to neurological damage or death, prompt recognition and therapy are mandatory. A history of nausea, weakness and progressive mental status impairment are frequently reported, whereas seizures, respiratory arrest and coma are generally found when the severity of hyponatremia worsens, i.e. dropping generally below 115 mEq/l, or the fall in plasma sodium levels is particularly rapid.

The recent availability of non-peptide antagonists of vasopressin-2 receptor (V_2-R), i.e. vaptans or "aquaretics", has enabled clinicians to target the underlying pathophysiology causing hyponatremia and, at the same time, has provided an adjunctive tool able to minimize the potential toxicities of the traditional therapeutic intervention (i.e. fluid restriction, hypertonic saline infusion and diuretics).[21-23] Regardless of the therapeutic approach, management priority must be given to a careful increase in sodium levels, according to a safety correcting rate of approximately 8 mEq/L per day [Table 2], in order to avoid osmotic demyelization in the pontine and extrapontine neurons.[24]

In conclusion, although water retention associated with NSAID is usually insignificant in healthy individuals since under normal euvolemic conditions prostaglandins play a negligible role in the preservation of renal circulation,[6] clinicians should implement strategies to prevent severe side effects in patients on DDAVP treatment. It is therefore mandatory to accurately inform these patients about the risks of co-treatments and to recommend therapeutic alternatives to NSAIDs when appropriate in order to improve desmopressin safety. This is of particular relevance for neurosurgeons and clinicians treating patients with pituitary disorders, since the incidence of diabetes insipidus (both transient and permanent) after trans-sphenoidal surgery is not negligible, being reported in up to 30% of patients, while the need for analgesic drugs is very common.[25]

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