Case Report

UNDULY ENHANCED RESPONSE TO TOLVAPTAN IN A WOMAN SHOWING SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION: AN INVESTIGATION OF POSSIBLE CAUSES

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ABSTRACT

Objective: To investigate possible causes of an excessive response to tolvaptan in a woman with syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Methods: A 32-year-old woman was admitted to our cardiologic unit 3 months after delivery for hypertension and severe hyponatremia (120 mEq/L). Two hyponatremic episodes had already been documented in her medical history. SIADH was diagnosed and treatment with tolvaptan, an arginine vasopressin (AVP) antagonist, was instituted. After the first 15-mg dose, excessive polyuria (1 L/hour) and a rapid increase in serum sodium (13 mEq/L in 8 hours) occurred, so that therapy was stopped and restarted 2 days later at a reduced dose (5 mg). This level was effective and well tolerated. To explore the possible pharmacokinetic and pharmacodynamic mechanisms underlying the patient's hyperresponsiveness, the following tests were carried out: (*1*) in vivo phenotyping of CYP3A4 activity, the cytochrome responsible for tolvaptan metabolism, with two probe drugs (omeprazole and dextromethorphan); and (*2*) search for mutations in genes involved in AVP signaling (*AVP*, *V2R*, *AQP2*, *OXT*).

Results: Neither phenotyping nor genotyping tests evidenced abnormalities capable of explaining the patient's enhanced response to tolvaptan, in that: (*1*) CYP3A4 activity was normal-to-high; and (*2*) genes coding for AVP, vasopressin-2 receptor, aquaporin-2, and oxytocin did not show any mutations.

Conclusion: This study excluded many, but not all, possible causes of hyperresponsiveness to tolvaptan. Two hypotheses concerning pretreatment AVP levels in SIADH patients are suggested to address future research. **(AACE Clinical Case Rep. 2017;3:e357-e360)**

Abbreviations:
3MM = 3-methoxy-morphinan; **AQP2** = aquaporin-2 water channel; **AVP** = arginine vasopressin; **CYP3A4** = cytochrome P450 CYP3A4; **DMT** = dextromethorphan; **OME** = omeprazole; **OXT** = oxytocin; **SIADH** = syndrome of inappropriate antidiuretic hormone secretion; **SUL** = omeprazole sulfone; **V2R** = vasopressin type 2 receptor

INTRODUCTION

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one of the most frequent causes of euvolemic hyponatremia (1). Conventional therapy, including fluid restriction and diuretics, are generally not tolerated well by patients. SALT-1 and SALT-2 trials (2) demonstrated that tolvaptan, a vasopressin receptor 2 antagonist, is a safe and effective alternative, provided that careful dose titration is applied. There is a serious risk of an excessively rapid increase in sodium serum concentrations resulting in osmotic demyelination, which may cause severe neurologic damage.

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CASE REPORT

A 32-year-old woman was admitted to our cardiologic unit for severe hyponatremia, presumed to be due to postpartum cardiomyopathy. Pregnancy had also been complicated by intra-uterine growth retardation (at the second trimester) and pre-eclampsia (at gestational week [GW] 34) associated with moderate hypertension (140/100 mm Hg), which was promptly treated with alpha-methyldopa 250 mg three times a day and nifedipine 10 mg three times a day. Delivery was induced with oxytocin at GW 37. As the birth date approached, marked fluid retention (positive water balance of 1,000 mL/day) was observed, together with slight hyponatremia (131 mEq/L) and chloremia at the lower normal limit (98 mEq/L). After the patient had been discharged, antihypertensive therapy was gradually suspended over a period of 2 months. No other pharmacologic treatments (including contraceptives) were instituted. Three months after delivery, she experienced weakness, numbness, headache, and pain at neck and knees, associated with severe hypertension (170/120 mm Hg) and severe hyponatremia (117 mEq/L) and was admitted to our unit for cardiologic evaluation. Of note, during two previous hospital admissions, hyponatremia had already been documented but overlooked by clinicians; the first, 14 years previously, was due to transient onset of scotomas (sodium = 132 mEq/L, chloride = 99 mEq/L, uric acid = 0.9 mg/dL) and the second, 10 years previously, for acute abdominal pain, without objective abdominal and gynecologic findings, which resolved spontaneously (sodium = 118 mEq/L, chloride = 87 mEq/L).

On admission, postpartum cardiomyopathy was excluded by ecocardiographic examination, which revealed normal heart volume and contractility (ejection fraction, 75%). The patient showed no clinical signs of fluid retention, despite laboratory signs of hemodilution, such as severe hyponatremia (120 mEq/L), hypochloremia (87 mEq/L), and hypouricemia (0.09 mEq/L). Plasma osmolality was low (233 mOsm/kg) and natriuria/24 hours elevated (299 mEq/24 hours). Urine osmolality was moderately high (488 mOsm/kg) in relation to serum osmolality but definitely higher than the cutoff of 100 mOsm/kg used to diagnose SIADH (1). A hydration test with isotonic saline (NaCl 0.9%) aggravated the hyponatremia (116 mEq/L) and induced typical signs of water retention (nausea, vomiting, fatigue, headache). Secondary causes of euvolemic hypo-osmolality—such as the use of diuretics, hypothyroidism, hypocortisolism, Sheehan syndrome, and renal insufficiency—were excluded by specific laboratory tests (thyroid-stimulating hormone, 2.26 mU/L; adrenocorticotropic hormone, 14 ng/mL; luteinizing hormone, 1.2 U/L; follicle-stimulating hormone, 4.9 U/L; prolactin, 17.3 μg/L; creatinine, 49 μmol/L; Chronic Kidney Disease–Epidemiology Collaboration creatinine clearance 123 mL/min), and a diagnosis of idiopathic SIADH (1) was made. Accordingly, therapy based on water restriction, oral NaCl supplements, and furosemide was instituted. This strategy led to gradual restoration of adequate sodium serum levels but was poorly tolerated by the patient (nausea, diarrhea, intolerance to water restriction). Specific therapy with an arginine vasopressin (AVP) receptor inhibitor (tolvaptan) was started, at the lowest recommended dose (15 mg/day). After administration of the first dose, the patient suffered a disproportionate pharmacologic effect, with considerable polyuria (1 L/hour) and a rapid increase in serum sodium (13 mEq/L in 8 hours), which was effectively controlled by abundant hydration with a 5% dextrose solution. Tolvaptan therapy was suspended and restarted 2 days later at a reduced dose of 5 mg. At the moment of writing, this dose still adequately maintains optimal levels of natremia, without dangerous side effects. Figure 1 shows the time course of sodium serum concentrations in relation to the various diagnostic and therapeutic interventions, and Figure 2 shows parallel changes in daily diuresis.

In an attempt to clarify the causes of such unusual hypersensitivity, further analyses were carried out to investigate possible pharmacokinetic or pharmacodynamic abnormalities. Since tolvaptan is primarily eliminated by cytochrome P450 CYP3A4 (CYP3A4) (3), CYP3A4 activity was phenotyped, with dextromethorphan (DMT) and omeprazole (OME) as probe drugs. After oral administration of 15 mg DMT and 20 mg OME, concentrations of 3-methoxy-morphinan (3MM) in 8-hour postdose urine and of OME sulfone (SUL) in 3-hour postdose plasma were determined by high-performance liquid chromatography methods (4,5), and the corresponding metabolic ratios were calculated: log(DMT/3MM) and log(OME/SUL). Methodologic details can be found in the cited papers. Quantification limits were 10 ng/mL for DMT and 3MM and 6 ng/mL for OME and SUL.

CYP3A4 metabolic activity, as expressed by both metabolic ratios, was higher than the mean reported in healthy populations (4,5) (Fig. 3), thus excluding impaired tolvaptan elimination as a pharmacokinetic cause of hypersensitivity. Possible causes of pharmacodynamic variability were also explored later, with particular reference to the mechanisms involved in AVP signaling. To explore the possibility that the patient's enhanced response to tolvaptan was due to mutations of genes coding for AVP, vasopressin type 2 receptor (V2R), aquaporin-2 water channel (AQP2), and oxytocin (OXT), a Sanger sequencing analysis was carried out (6). However, genetic analyses proved that all candidate genes were wild type, thus leaving clinical observations unexplained.

DISCUSSION

Our patient fulfilled all major diagnostic criteria for SIADH (1), in particular: (*1*) serum osmolality was <275 mOsm/kg; (*2*) she was clinically euvolemic; (*3*) urine

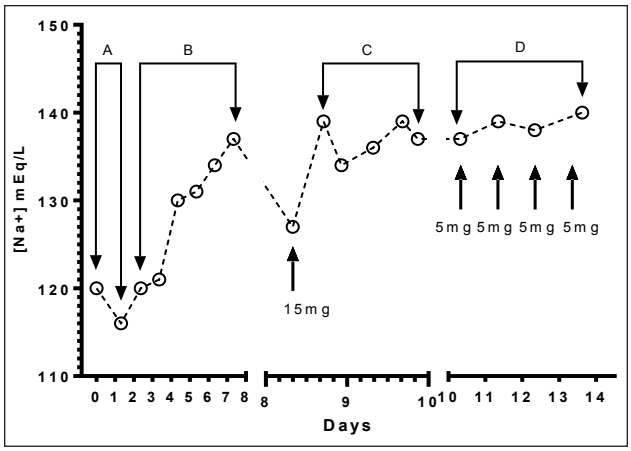

Fig. 1. Time-course of sodium plasma concentrations in relation to diagnostic and therapeutic interventions. (*A*) Hydration test with 0.9% saline. (*B*) Water restriction plus oral NaCl plus furosemide. (*C*) Hydration with 5% dextrose after a 15-mg tolvaptan dose, which produced abundant diuresis. (*D*) Free hydration plus 5 mg tolvaptan every day.

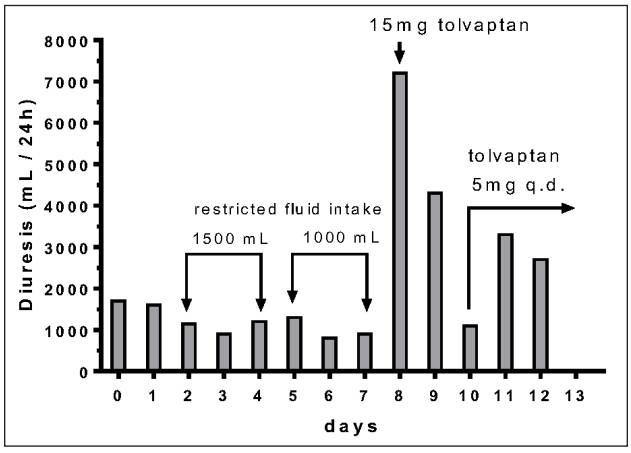

Fig. 2. Time course of diuresis. Timing of therapeutic interventions are indicated by arrows. *q.d.* = every day.

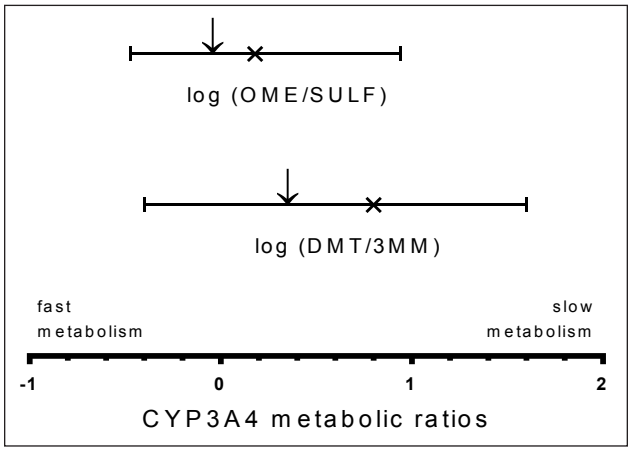

Fig. 3. Cytochrome P450 CYP3A4 activity measured with omeprazole (OME) and dextromethorphan (DMT) as probe drugs. Corresponding metabolic ratios expressed as log ratios between drug and metabolite concentrations in plasma or urine, as required (see text). Upper and lower segments: normal log(OME/SULF) and log(DMT/3MM) ranges. Mean normal values indicated by ×; arrows indicate metabolic ratios determined in our patient. *3MM* = 3-methoxy-morphinan; *SULF* = omeprazole sulfone.

osmolality was >100 mOsm/kg; (*4*) no laboratory data evidenced adrenal, thyroid, pituitary, or renal insufficiency; and (*5*) no drugs were administered (e.g., diuretics). Also, three supplemental criteria were verified: (*1*) hypouricemia; (*2*) failure to correct hyponatremia after 0.9% saline infusion; and (*3*) correction of hyponatremia through fluid restriction. Initial therapy based on fluid restriction was effective in restoring normal sodium serum levels, but the patient developed nausea and diarrhea, probably due to oral NaCl supplements. Therefore, she was shifted to tolvaptan, an AVP receptor inhibitor, at the standard 15-mg dose, which, however, produced an unusually marked diuretic effect.

The ability of tolvaptan to increase sodium serum concentrations is quite variable among patients with SIADH, so that those who do not meet the target sodium concentration of 135 mEq/L after the starting dose of 15 mg/day can be treated with 30 mg or 60 mg daily, as necessary. Gradual dose titration is recommended, since a too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) may result in osmotic demyelination and life-threatening neurologic manifestations. Our patient exhibited severe hyponatremia on admission (120 mEq/L); after a single 15-mg dose of tolvaptan, sodium concentrations increased by 13 mEq/L in 8 hours, but thanks to the prompt institution of hydration therapy, she did not develop neurologic symptoms. To our knowledge, only one similar case has been reported in the literature, regarding a 51-year-old woman who showed a rapid increase in urine output and symptomatic hypotension after a 15-mg dose of tolvaptan and was then effectively and safely treated with a reduced dose of 4.5 mg (7).

In the SALT-1 and SALT-2 trials, 4 of the 223 patients (1.8%) exceeded the desirable rate of sodium correction (>0.5 mEq/L/hour) during the first 24 hours of the study. It is therefore evident that a subgroup of patients with SIADH may be hyperresponsive to tolvaptan, for reasons not yet clarified.

To investigate the causes of the enhanced response in our patient, we explored the pharmacokinetic and/or pharmacodynamic mechanisms which might have been involved. First, we measured the in vivo activity of CYP3A4, responsible for tolvaptan metabolism, with two probe drugs, OME and DMT. Both indicated that CYP3A4 activity was higher than the mean reported in healthy subjects, thus excluding a pharmacokinetic cause of hyperresponsiveness.

We then looked for mutations of macromolecules possibly involved in the tolvaptan effect. AVP increases water permeability along the collecting duct by binding the V2 receptor which, in turn, triggers short-term upregulation of the AQP2 water channel and long-term AQP2 protein transcription. In addition, the role of OXT in inducing SIADH was suggested by two (now dated) reports of water intoxication following OXT infusion (8,9) and by

a more recent experimental study (10) that demonstrated that OXT can bind the V2 receptor and stimulate water permeability of the collecting duct and that its effect can be blocked by a V2 receptor inhibitor. However, neither agonists of V2R (AVP and OXT) nor the molecules involved in signal transduction (V2R and AQP2) revealed any genetic abnormalities.

In principle, the response to an antagonist depends on a number of factors, such as relative concentrations of the agonist (i.e., AVP) and antagonist (i.e., tolvaptan), number and affinity of receptors (i.e., V2R), and changes in postreceptor mechanisms (i.e., AQP2). The results in our patient tend to exclude excessive exposure to tolvaptan (CYP3A4 activity), changes in molecular structures of V2R or AVP/OXT (no gene mutations) and in signal transduction (no AQP2 mutations). Accordingly, hyperresponsiveness to tolvaptan may be due to lower plasma AVP concentrations or decreased V2 receptor number. Indeed, Vaghasiya et al (11) reported an inverse correlation between baseline AVP levels and natremic response to tolvaptan in SIADH patients, suggesting that a more complete V2R blockade occurs when AVP levels are low.

Another possibility is that prolonged exposure to AVP plasma concentrations may have downregulated the patient's V2 receptors by a ligand-induced internalization mechanism. This adaptive mechanism has been demonstrated in rats (12,13) and is considered responsible for the progressive loss of antidiuretic effect of AVP observed in humans during prolonged AVP infusion (the "renal escape from antidiuresis" phenomenon) (14). According to the occupancy receptor theory, a reduced number of receptors increases the effect of an antagonist. Both these hypotheses foresee an increased V2 receptor occupancy by tolvaptan but with opposite mechanisms, one implying relatively low and the other relatively high AVP plasma levels.

We did not measure the AVP plasma levels in our patient because the AVP concentration is not a criterion for diagnosing SIADH and the AVP assay has methodologic limitations (15). However, since a direct correlation has been demonstrated between urine osmolality and AVP plasma levels (16), our finding of a moderate increase in urine osmolality (488 mOsm/kg) may have reflected a moderate increase in AVP plasma levels and a greater susceptibility to V2R block.

CONCLUSION

A few SIADH patients may exhibit an unusually intense response to tolvaptan and require doses much lower than the lowest recommended (15 mg). Although we could not positively identify the cause of hyperresponsiveness in our patient, we did exclude some important pharmacokinetic and pharmacodynamic mechanisms. Further experimental work is needed to clarify the relationship between baseline AVP levels in SIADH patients and response to AVP antagonists.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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