Case Reports

Verapamil-Induced "Primary" Polydipsia

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Abstract. An 11-month-old male infant with recurrent supraventricular tachycardia (SVT) was treated with oral verapamil. Shortly thereafter he developed marked changes in behavior including lethargy, intensely increased thirst and urination, and irritability when denied fluids. "Primary" polydipsia was diagnosed following an evaluation which showed no evidence of adrenal insufficiency, diabetes insipidus, diabetes mellitus, hyperosmolality, or renal disease. The symptoms resolved 1 week after verapamil was discontinued.

Key words: Calcium channel — Polyuria — Primary polydipsia — Verapamil

Adverse cardiovascular side effects following the use of verapamil are common, and headache, dizziness, nausea, and constipation occur less often. Previous reports have discussed effects of calcium channel blockers on anterior pituitary function; hypoprolactinemia associated with verapamil has been well characterized [7, 10]. Other calcium channel blockers (i.e., nifedipine and diltiazem) may not alter anterior pituitary secretory dynamics [11–13]. A MEDLINE search of the literature could find no references associated with calcium channel blockers and posterior pituitary function, specifically in terms of thirst and fluid regulation.

We report an infant who developed primary polydipsia during chronic treatment of supraventricular tachycardia (SVT) with oral verapamil.

Case Report

Supraventricular tachycardia was diagnosed in a 6-week-old male infant at our Hospital. He was born vertex and vaginally, but precipitously after 40–41 weeks' gestation, to a 27-year-old gravida 3 para 2 abortion 1 mother whose pregnancy was complicated by a mild diarrheal illness. The birth weight was 2815 g. At age 6 weeks he presented with vomiting and poor feeding. The electrocardiogram (ECG) showed narrow QRS tachycardia at 305 bpm. Noninvasive evaluation suggested the infant had atrioventricular (A-V) reentrant SVT using a concealed accessory pathway for retrograde conduction. There was no evidence of other heart disease. SVT was treated orally with digoxin after successful conversion to sinus rhythm with adenosine. Verapamil was added after 3 months because of recurrence of the arrhythmia. The patient did well, and both medications were discontinued by 6 months of age. SVT recurred at age 11 months, and verapamil alone was administered at a dose of 15 mg tid (5 mg/kg per day).

Shortly thereafter the patient began to experience markedly increased thirst and urination as well as increasing listlessness and lethargy. His parents estimated his daily fluid intake at home at 88 oz (2640 ml), which was 2.5 times his estimated daily requirements. He stopped drinking formula and preferred water or Gatorade. He demonstrated intense thirst and drank continuously in the clinic, although the fluid consumption was not formally quantitated; he had marked thirst and irritability during a formal fluid deprivation study. The physical examination did not demonstrate abnormalities or evidence of sexual ambiguity or precocity. Routine baseline serum and urine analyses failed to demonstrate metabolic abnormalities. There was no evidence of thyroid dysfunction (T₄ 7.4 μg/dl, TSH 1.6 μIU/ml), diabetes mellitus (no glycosuria, serum glucose 91 mg/dl), hypercalcemia (calcium 9.9 mg/dl), or salt wasting adrenal insufficiency (cortisol 10.1 μg/dl, plasma renin activity 1.0 ng/ml per hour).

Table 1 shows the results of the water deprivation study. Renal ultrasonography and hypothalamic-pituitary magnetic resonance imaging were normal.

At age 14 months, verapamil was discontinued, and oral digoxin (10 μg/kg per day) was restarted. Within 1 week all symptoms of polydipsia, polyuria, and lethargy resolved. The family has refused to rechallenge the patient with oral verapamil.

Discussion

Disorders manifested by polyuria may be categorized broadly into hypertonic and hypotonic condi-
tions. The former, associated with increased osmotic renal solute loads, include diabetes mellitus, hypercalcemia, and conditions associated with renal "salt-wasting," such as intrinsic renal disease and adrenal insufficiency (i.e. forms of congenital adrenal hyperplasia and Addison's disease). Hypotonic polyuria is associated with relative excessive free water loss; causes include central and nephropathic diabetes insipidus, volume overload, and central polydipsia. Given an intact thirst mechanism, these disorders, except central polydipsia (and volume overload), feature a compensatory increase in thirst ("secondary" polydipsia). Central or "primary" polydipsia therefore is a disorder characterized by a primary increase in thirst leading to appropriate polyuria to prevent water intoxication.

Verapamil is a synthetic alkylamine that binds dihydropyridine receptors and blocks L-type calcium channel currents. These channels occur in cardiovascular as well as neural and endocrine tissues. Verapamil is well absorbed orally, has significant first-pass metabolism in the liver, and is excreted mostly by the kidney. With chronic use the elimination half-life may approach 12 hours.

In this patient, verapamil apparently induced effects on the hypothalamic thirst center leading to polydipsia. The use of the term "primary" to describe this polydipsia may be debated, as the thirst occurred following oral verapamil therapy. Although drug-induced, central polydipsia causing suppression of antidiuretic hormone (ADH) secretion has been described [1], our patient did not have ADH suppression. In addition, primary polydipsia can be idiopathic, associated with central nervous system (CNS) lesions, or psychogenic in origin; the latter is reported rarely in children [8]. These other causes of polydipsia and polyuria were excluded by the baseline and 7-hour water deprivation studies (Table 1). Because adrenal mineralocorticoid synthesis is regulated primarily by the renin-angiotensin axis, Plasma renin activity (PRA) is elevated in conditions associated with urinary salt loss. The patient's age at symptom onset, lack of sexual precocity, and normal PRA do not support a diagnosis of salt-losing congenital adrenal hyperplasia; Addison's disease was excluded by the normal cortisol concentration.

During 7 hours of supervised water deprivation, the endocrinologically intact individual experiences diminished urinary output and increased urine osmolality while maintaining normal serum osmolality and sodium concentrations. This balance is accomplished, in part, by an increase in ADH secretion. Patients with renal concentrating defects, such as neurogenic or nephropathic diabetes insipidus, are unable to significantly decrease urine volume or increase urine osmolality; in such patients the ratio of urine osmolality/serum osmolality is not greater than 1.5 [4]. Neurogenic diabetes insipidus also is excluded in this patient because of the measured normal rise in ADH with fluid deprivation.

In our patient, no CNS or renal lesions were detected. The most compelling evidence that his symptoms were related to verapamil was the temporal association of symptom onset and resolution with verapamil administration and its subsequent discontinuation.

Several studies have suggested that verapamil may modulate anterior pituitary function, especially in relation to prolactin secretion [7, 10]; verapamil-induced galactorrhea has been described [5]. The mechanism may be due to diminished CNS release of dopamine at the tuberoinfundibular level rather than a direct effect of verapamil on pituitary lactotrophs [6]. Studies of other calcium channel blockers have not shown changes in growth hormone, thyrotropin, or gonadotropin secretion [11-13]. Posterior pituitary dysfunction with verapamil has not been reported, and the complete effects of verapamil on neuroendocrine calcium channels are unknown. Although we propose an effect of verapamil to primarily increase thirst in our patient, intraventricular infusion of diltiazem in animals has produced anorexia [3], and other studies have implicated hypothalamic calcium channels in the regulation of sleep and of the corticotropin-releasing hormone-secreting neurons, which also influence ADH secretion [2, 9].

To our knowledge, this case of primary poly-

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**Table 1. Results of water deprivation study in the patient**

<table>
<thead>
<tr>
<th>Duration of &quot;thirst&quot;</th>
<th>Weight (kg)</th>
<th>Sodium (mmol/L)</th>
<th>Osm(S) (mOsm/kg)</th>
<th>Osm(U) (mOsm/kg)</th>
<th>U/S (ml/h)</th>
<th>ADH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>11.1</td>
<td>138</td>
<td>292</td>
<td>703</td>
<td>2.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Five hours</td>
<td>10.8</td>
<td>140</td>
<td>291</td>
<td>882</td>
<td>3.0</td>
<td>12</td>
</tr>
<tr>
<td>Seven hours</td>
<td>10.7</td>
<td>140</td>
<td>294</td>
<td>925</td>
<td>3.1</td>
<td>8</td>
</tr>
</tbody>
</table>

Osm(S), serum osmolality; Osm(U), urine osmolality; U/S, urine/serum osmolality ratio; ADH, antidiuretic hormone.