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SHORT COMMUNICATION

Finally an Oral V2 Selective Vasopressin Antagonist

Nasr Anaizi

Department of Pharmacology, University of Rochester, Rochester, New York, USA

Email: anaizi1@gmail.com

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Hypervolemic hyponatremia is a serious complication of edematous diseases such as congestive heart failure and hepatic cirrhosis; it is usually a harbinger of prolonged hospitalization and increased risk of mortality. Euvolemic hyponatremia, on the other hand, is associated with conditions such as syndrome of inappropriate ADH (SIADH) (1) in which vasopressin activity is inappropriately elevated. Vasopressin, often referred to as arginine vasopressin (AVP) or antidiuretic hormone (ADH), is a peptide hormone that plays a critical role in renal hemodynamics and in the maintenance of water balance. There are three known AVP receptors: V_{1a}, V_{1b}, and V_2. All three receptors are coupled to the G-protein and while V_{1a} mediates the hormone's vasomotor effect, V_2 mediates its water absorption (antidiuretic) effect on the distal nephron segments (2).

In addition to treating the underlying disease whenever possible, the management of hyponatremia has traditionally relied for the most part on restricting water intake, discontinuation of drugs known to cause hyponatremia, and in the case of SIADH on the off-label use of demeclocyline. Slow infusion of hypertonic saline is usually reserved for symptomatic patients with Na^+ levels below 125 mEq/L since rapid correction of serum osmolality carries a significant risk of the osmotic demyelination syndrome (ODS) (3).

However, recent years have witnessed the emergence of a new class of drugs, the vasopressin antagonists that are more specific for this potentially life-threatening condition (4). In 2005 the US FDA approved conivaptan (Vaprisol) for intravenous use in hospitalized, euvolemic and hypervolemic hyponatremic patients. Conivaptan is a non-peptide antagonist of arginine vasopressin receptor subtypes V_1 and V_2 which has proven effective in raising serum Na^+ by >6 mEq/L in over 70% of patients (5,6). However its use is mostly limited to euvolemic patients and it is not to be used in patients with CHF unless the benefit of raising serum Na level outweighs the increase risk of adverse events. The clinical utility of conivaptan is further limited by significant drug-drug interactions involving an extensive list of potent CYP3A4 inhibitors such as the azole antifungals and clarithromycin. The various restrictions imposed on the use of conivaptan have severely limited its clinical utility and spurred the development of a more clinician-friendly agent in the same class (7). After a multicenter phase III trial (8), an oral, V_2-selective vasopressin antagonist has now become available with the recent approval (May 2009) by US FDA of tolvaptan (Samsca). The V_2 receptor is responsible for the ADH-mediated increase in water reabsorption in the distal nephron segments. Selective blockade of V_2 results in water diuresis (aquaresis).

According to the FDA labeling (9) tolvaptan is indicated

for the treatment of "clinically significant hypervolemic and euvolemic hyponatremia [serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction], including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)". It is not indicated for patients "requiring intervention to raise serum sodium urgently". However, therapy initiation and dose titration of tolvaptan should take place in the hospital due to the need for electrolyte, neurologic and hemodynamic monitoring. The initial dose is 15 mg once daily which may be increased gradually as necessary up to a maximum of 60 mg per day. Once an adequate response is achieved therapy may be continued on outpatient basis. While taking this medication, patients should be advised to respond normally to thirst by ingesting fluid, and when the drug is discontinued fluid restriction should be re-established.

The most common side effects associated with tolvaptan are thirst, dry mouth, asthenia (loss of strength), constipation, pollakiuria or polyuria, and hyperglycemia. Tolvaptan is a substrate and inhibitor of CYP 3A and P-glycoprotein and should be used with caution with drugs that can have a significant effect on its absorption and/or metabolism.

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