HYPONATREMIA

# Prolonged use of the vasopressin antagonist tolvaptan is a safe and effective treatment for hyponatremia

Oral administration of the vasopressin V2-receptor antagonist tolvaptan is safe and effective for the treatment of chronic hyponatremia in the long term, according to the results of the SALTWATER trial recently reported in the *Journal of the American Society of Nephrology*.

"Hyponatremia is a common electrolyte disorder in clinical medicine and the tools available to treat it have been unsatisfactory," states lead author Tomas Berl. Although two randomized, placebo-controlled, double-blind phase III studies (SALT-1 and SALT-2) had previously shown that short-term (≤30-day) administration of tolvaptan safely increased serum sodium level in patients with euvolemic or hypervolemic hyponatremia, effects of long-term treatment were unknown.

The SALTWATER study was an open-label extension of the SALT-1 and SALT-2 studies. "Given the short-term efficacy [of tolvaptan] demonstrated in the SALT-1 and SALT-2 trials, it was not possible to continue with a placebo arm," explains Berl. Patients were eligible to take part in SALTWATER if they had successfully participated in SALT-1 or SALT-2 and still required therapy.

In total, 111 patients were enrolled and received oral tolvaptan therapy (15 mg daily initially, for a maximum of 214 weeks) in SALTWATER; 84.7% of these patients had hyponatremia. The cause of hyponatremia was congestive heart failure (CHF) in 29.7% of patients, cirrhosis in 18.0% of patients, and the syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) or another cause in 52.3% of patients. As baseline characteristics did not differ between patients who had been on tolvaptan or placebo in SALT-1 or SALT-2, all patients in SALTWATER were analyzed together.

During a mean follow-up time of 701 days on tolvaptan therapy (equivalent to a total observation time of 212 patient-years), 105 of 111 patients (94.6%) experienced an adverse event. "Because most patients with hyponatremia with CHF and cirrhosis have severe underlying disease and because neoplastic disease is relatively common in patients with euvolemia, it is not surprising that nearly all patients at some time or another were found to have an adverse event," state the authors. The most common adverse events were similar to those reported in short-term studies of tolvaptan, and included thirst, dry mouth and polyuria. Ten serious adverse events occurred that were considered to be possibly or probably related to tolvaptan use; the relationship was thought to be possible rather than probable for nine of these events, with the researchers noting that the patient involved had multiple associated medical problems that might have been responsible. Six occasions were recorded where adverse events potentially related to tolvaptan administration led to the withdrawal of the treatment. Overall, 19 patients died during tolvaptan treatment, a result corresponding to nine deaths per 100 patient-years of tolvaptan exposure; one of these deaths (severe hepatorenal syndrome on day 53) was deemed to be possibly related to study medication use.

The researchers found that mean serum sodium level increased from 130.8 ± 4.4 mmol/l at baseline to above 135 mmol/l after 14 days of treatment, and remained within the normal range for the rest of the study. Hypernatremia occurred in 12 patients but was readily reversible in 11 of these and resulted in drug discontinuation in only one patient.

"This report will provide confidence for placing patients with chronic hyponatremia due to SIADH or hypervolemic conditions such as CHF and cirrhosis on a V2-receptor antagonist," concludes Berl. "Future studies need to be directed at establishing whether such a treatment affects hospitalization rates, prolongs survival and improves patient well-being."

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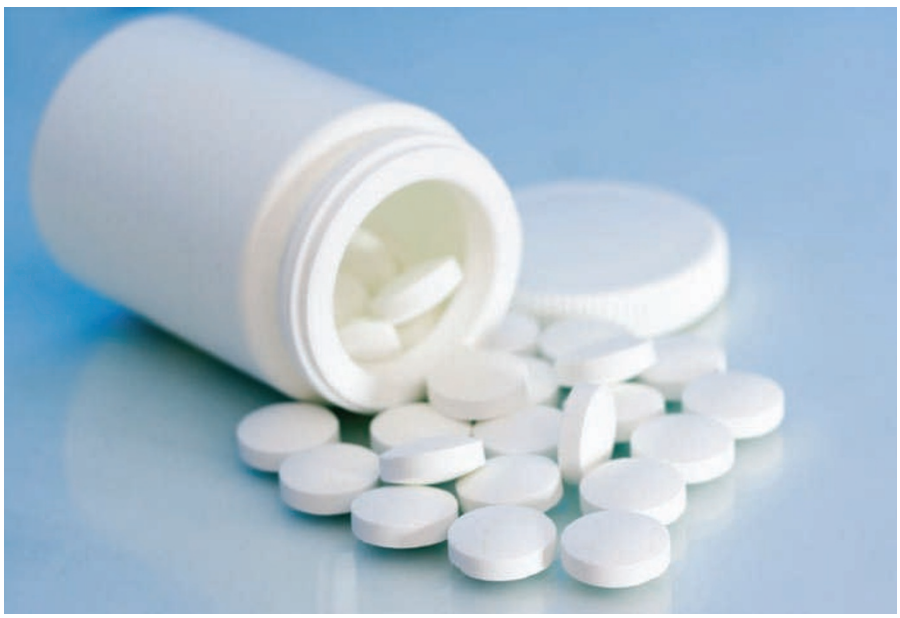

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