High sensitivity to tolvaptan in paraneoplastic syndrome of inappropriate ADH secretion (SIADH)

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) not only induces uncharacteristic clinical symptoms but also increases morbidity and mortality [1, 2]. The recent introduction of vaptans acting as V2-receptor antagonists considerably improved the unconvincing results of conventional treatment consisting of fluid restriction potentially combined with sodium supplementation and/or demeclocycline therapy [3]. With their high therapeutic potency, the risk for an unduly rapid correction of chronic SIADH increases, which is associated with a life-threatening condition, central pontine myelinolysis [4]. Chronic SIADH is observed in many cancer types but the sensitivity toward vaptan therapy is currently not systematically investigated.

We thus followed 13 patients with paraneoplastic SIADH (4 male and 9 female, aged 59–88 years; 7 patients with small-cell lung cancer (SCLC) and 1 patient each with pulmonary tumor of undefined histopathology, non-SCLC, esophageal carcinoma, cholangiocarcinoma, myeloma and liposarcoma) as to their initial and chronic response to vaptan therapy. Diagnosis was based on severe persistent hyponatremia, decreased plasma osmolality, raised urinary osmolality or urinary sodium excretion and the absence of other causes. None of the patients sodium levels were normalized under pretreatment with conventional therapy.

A single dose of 15 mg tolvaptan in a patient with SCLC increased serum sodium levels from 114 to 131 mmol/l within 24 h, a finding confirmed in a second patient. Thus, we halved the initial tolvaptan dose (7.5 mg) resulting in a maximal 24-h serum sodium increase of 11 mmol/l (baseline serum sodium ranging from 110 to 126 mmol/l, plasma osmolality from 235 to 277 mOsmol/l, urinary osmolality from 297 to 834 mOsmol/l). Serum sodium levels normalized in 11 patients under alternate day treatment with 7.5 mg tolvaptan despite stopping fluid restriction and demeclocycline. Only two subjects needed adaptation with higher long-term tolvaptan doses (15 and 30 mg/day) to stabilize serum sodium levels >130 mmol/l.

Six of our patients died but in none of them a direct relation to tolvaptan therapy was identified. The longest survival under treatment was 4 months with sodium levels in the normal range. Interestingly, hyponatremia (114 and 117 mmol/l) promptly reappeared in this patient when tolvaptan therapy was intermittently stopped.

These data suggest a high sensitivity of patients with paraneoplastic SIADH toward tolvaptan. They support a previous study using the i.v. conivaptan to prevent hyponatremia and a recent therapeutic suggestion in SIADH by Palm et al. [5, 6]. After reducing the initial tolvaptan dose to 7.5 mg and stopping fluid restriction in parallel, we did not experience any dangerously rapid increase in serum sodium levels. Thus, patients with paraneoplastic SIADH should be started with lower than suggested doses of tolvaptan, which upon adaptation offer a safe and sustainable therapy to correct hyponatremia.

S. Kenz1, C. S. Haas2, S. C. Werth2, S. Bohnet3 & G. Brabant1,2*
1Department of Endocrinology, The Christie, Manchester, UK,
2Departments of Medicine I, Medicine III, University of Lübeck, Lübeck, Germany
(*E-mail: Georg.brabant@uk-sh.de)

disclosure
The authors declare no conflict of interest.

references
doi:10.1093/annonc/mdr431
Published online 21 March 2011