Editorial Comments

The vaptans: just landed. But how was the trip?

Peter Gross

Department of Medicine III, Universitätsklinikum Carl Gustav Carus Fetscherstraße 74, 01307 Dresden, Germany

Correspondence and offprint requests to: Peter Gross; E-mail: peter.gross@uniklinikum-dresden.de

Vaptans is a collective term for a novel class of compounds: orally available vasopressin antagonists. They have been developed primarily for the treatment of hyponatraemia. Although this is a plausible concept, the details of the treatment could be less straightforward than it might appear. For instance, the secondary thirst of a vaptan treatment [1] could increase the fluid intake substantially and thereby jeopardize the therapeutic effect. On the other hand, overcorrection of hyponatraemia might be difficult to prevent once the vaptan is used in the real world (overcorrection: ≥0.5 mmol/L/h in the setting of chronic hyponatraemia). Until recently, no such problems had surfaced—but the use of vaptans had been restricted to binding scientific protocols. This has changed, and two approved vaptans are now available for general use [conivaptan, only available as an intravenous (i.v.) preparation; tolvaptan, a tablet]. In this issue of the journal, Velez et al. describe the treatment of hyponatraemia using conivaptan as a routine measure in their hospital [2]. How did the vaptan do?

The i.v. conivaptan, given as recommended by the manufacturer, was indeed effective. All 18 patients diagnosed with the syndrome of inadequate antidiuresis (SIAD) responded. All showed a clear increase of the serum sodium level: the mean value rose from 121.7 ± 3.3 mmol/L at baseline to 129.2 ± 2.6 mmol/L within the first 24 h of treatment. Concomitantly, the urinary osmolality dropped in all, from 476.8 ± 132 to 243.2 ± 151.8 m0sm/kg. As expected, the urinary output increased; in fact, it almost doubled from 1.5 ± 0.29 to 2.7 ± 0.5 L/day. Due to these robust responses, the mean treatment time (the duration of conivaptan infusions) could be kept down at only 13 h. The improved serum sodium level was well maintained even at 48 and 72 h after discontinuation of conivaptan. (All patients were on a fluid restriction to 1 L/day).

Finally, the authors succeeded in predicting the individual correction rate of the given hyponatraemia: the lower the baseline serum sodium and the higher the estimated glomerular filtration rate (eGFR), the faster the correction rate which is compatible with a previously published work [3]. Considering our previous standard therapy for hyponatraemia—time-consuming and frustrating fluid restrictions—conivaptan was clearly more efficient, more specific and more time saving. I assume this is what a hospital administrator must consider the equivalent of paradise. But was it ideal to the doctor, too?

From a medical standpoint, safety could be an issue. In this respect, Figure 1 of [2] shows that 5 or 6 of the 18 patients had a correction rate of 10 mmol/L or more in the first 24 h, disturbingly close to the limit. In four patients, the authors had to interrupt the infusions of conivaptan prematurely because of a too rapid correction. Since the paper does not give a very detailed report, it is possible that not all of these four patients belong to the group of six patients; in other words, the incidence of potentially risky treatments may have been larger than six out of 18. Fortunately, in most patients, the serum sodium was measured every 6 h—which must have caused extra ‘discomfort’. But without this extra attention, the four patients who had their infusions interrupted might have progressed to severe overcorrection. In a single patient, the serum sodium apparently rose by 16 mmol/L (from 119 to 135 mmol/L) within the first 24 h—not quite a safe result if this patient would have had chronic hyponatraemia. One patient experienced a drop of the systolic blood pressure from 110 to 88 mmHg, necessitating a saline infusion. In two patients, the serum creatinine increased ≥25%, though this was still within normal limits. Clearly then, adequate safety was problematic. We seem to be paying a price for the efficiency of conivaptan in the majority of patients by overcorrection in some. Perhaps, it would have helped to avoid these unwanted effects if a more liberal fluid intake had been permitted or if the dose of conivaptan had been lower. But for the time being, meticulous care and close follow-up of the patients are strictly indicated to prevent risky correction rates.

Isn’t there something else missing? Wasn’t the doctor the one who alleviated the symptoms and prevented the suffering? Well then, how did conivaptan benefit the well-being of the patients? Or was it basically given to correct the numbers printed on lab reports? How symptomatic were these patients at baseline? Did they have confusion, headache, loss of balance or impaired memory, and if so, what effect did conivaptan have on these symptoms? What did the patients have to say about the thirst in response to conivaptan? Were there any other indications for conivaptan other than symptoms and complaints, such as prevention of relapse, reduction in the length of hospital stay in refractory cases or prophylaxis against the worsening of hyponatrae-
milia? What was the long-term outcome?—Unfortunately, all of these important issues are left unanswered by the present report [2]. The authors performed only a retrospective analysis; in this analysis, conivaptan had been given in the course of routine treatment months before. We may speculate that the records just failed to convey enough detail to answer our questions. But we surely would have liked to know.

For the time being, conivaptan was shown to be an efficient agent to correct the hyponatraemia of SIAD in everyday life. Its application must be watched closely in a hospital setting to prevent overcorrection. The benefit to the patients’ well-being and the most convincing indications for conivaptan are not sufficiently clear yet and await future studies.

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References

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African Americans compared to Senegalese—same number of glomeruli, but greater glomerular size. What does this tell us?

Eberhard Ritz and Nadezda Koleganova

Correspondence and offprint requests to: Eberhard Ritz; E-mail: prof.e.ritz@t-online.de

Based on observations documenting a relation between birth weight and mortality or cardiovascular events at adult age many years ago, Barker et al. had put forward the hypothesis that prenatal factors may have an impact on organogenesis [1] (‘prenatal programming’) and determine both cardiovascular [2,3] events and hypertension [4] as well as renal risk at adult age [5]. More specifically, Brenner et al. have postulated that an endowment with a lower number of nephrons predisposed to hypertension and chronic kidney disease [6]. In humans, the number of glomeruli at the time of birth is finite and reflects prenatal growth. Postnatal glomerulogenesis does not occur in humans in contrast to rats. One risk factor for low numbers of glomeruli is low birth weight [7].

A series of human studies has linked low birth weight (as an index of poor intrauterine organ growth) with hypertension [4,8], particularly when followed by postnatal catch-up growth [9,10]. Higher blood pressure values are seen within 1 year after birth [11,12] and have been well documented in adolescents [13]. Blood pressure in individuals with a history of low birth weight is characterized by salt sensitivity [14].

Low birth weight is also associated with the risk of higher levels of albuminuria [15], with low glomerular filtration rate (GFR) [16], and with higher risks of chronic kidney disease (CKD) [17] and end-stage renal disease (ESRD) [18] as well as with higher rates of progression of established renal disease [19,20]. So, the issue of low birth weight does have renal relevance. In the ideal world, nephrologists should know the birth weight of their patients (although unfortunately this is more frequently than not unknown to our patients).

The postulate of Brenner et al. [6] was solidly confirmed by the observation of a relation between the low number of nephrons on the one and the presence of hypertension on the other hand [21,22]. But matters are not as simple as they appeared initially as again illustrated by the study of McNamara et al. in the present issue of Nephrol Dial Transplant [23].

The authors compared the number and size of glomeruli of Senegalese individuals and African American. The authors examined the relation between these indices and body weight and (at least in African American) blood pressure. The data confirm previous findings of the same group that—in contrast to Caucasians—no correlation is found between glomerular number and blood pressure in individuals of African origin [24]. There must be a fundamental difference between Africans and non-Africans in this respect. The observation is particularly plausible since Rostand et al. [25] had previously shown that, in African American (in contrast to non-Africans), birth weight was not a predictor of blood pressure in adult life.