The vaptans ante portas: a status report

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On 25 June 2008 the US Food and Drug Administration held a public Advisory Committee Meeting of its Cardiovascular and Renal Drugs Division on Tolvaptan (NDA 22-275), the first oral vasopressin antagonist to apply for licensing (http://www.fda.gov/ohrms/dockets/ac/CVDer08.html# CardiovascularRenal). Based on the comments made, we may now expect that tolvaptan will make it to the pharmacies soon. Over the last few years, we have been shown repeated evidence that vaptans shall be helpful (and safe) in the treatment of chronic hyponatraemia under most, though not all, circumstances [1,2]. Assuming that this scenario will come true, is it time to lean back and consider the issues surrounding the vaptans resolved? Not really.

Will it pay to use vaptans?

Surprisingly, we do not really know. One publication was able to demonstrate that hyponatraemia was a predictor of (increased) medical costs at 6 and 12 months [3], but this does not necessarily prove that costs will decrease in response to treatment of hyponatraemia with vaptans. Another, and perhaps more helpful new aspect derives from observations by the group of Decaux in Brussels [4]. The authors used neurocognitive testing to examine if mild chronic hyponatraemia in elderly patients (n = 16; 128 ± 3 mmol/L) changed mental function. The tests were done in hyponatraemia and again in normonatraemia in the same individuals. Hyponatraemia impaired concentration, memory and reaction time; in addition, it was associated with an increased incidence of falls. In the elderly falls may result in fractures, disability and complications. In this way the data [4]—if confirmed by others—would suggest that it pays to treat even mild-to-moderate chronic hyponatraemia.

Which hyponatraemias must not be treated with vaptan?

It is now clear that vaptans shall be reliable agents to correct the hyponatraemias of ‘euvoalaemic’ (SIADH-type) and ‘hypervolaemic’ (oedematous cardiac failure and liver cirrhosis) states [1,2]. In contrast, in ‘hypovolaemic’ hyponatraemic states—e.g. after diarrhoea, vomiting or overly ambitious diuretic therapy—vaptans are contraindicated. Instead, the replacement of the ECF lost by isotonic saline is the way to go. Cerebral salt wasting [5]—when it does occur—is also no candidate for vaptan treatment but should receive volume replacement with isotonic saline.

Why are there treatment failures with vaptans?

In all studies of hyponatraemia it was found that ∼10–20% of patients showed no response to vaptan. The reasons for this deficient response have not been studied in detail yet. Obvious potential explanations—such as excessive drinking or pharmacokinetic abnormalities—may account for some of these failures. In other cases a more intriguing recent proposal may apply [6]. The group of Stephen E. Gitelman was able to ascribe the hyponatraemia in two infants who had no measurable ADH to missense mutations of the V2 vasopressin receptor gene [6]. These mutations resulted in constitutive activation of the receptor. This is a very attractive proposal for two reasons: (a) as demonstrated by Decaux et al., such mutated V2 receptors may be unresponsive to vaptans [7] and (b) it had been found in several observational studies of hyponatraemia in the past that there were always some 10% of patients without measurable vasopressin—usually attributed to suspected insensitivity of the assays used in those days. On the other hand, the authors [6,7] cannot explain why such patients would continue drinking in the face of hypoosmolality—something that is indispensable to the generation of a hyponatraemia—plus they have not been able to dispel concerns that these constitutively activated V2 R mutations may be exceedingly rare. So the real importance of the findings is presently uncertain. Other proposals such as an increased renal responsiveness to vasopressin [8] or PKD 1 haploinsufficiency [9] may yet turn out to be relevant to hyponatraemia in the presence of very low levels of ADH. Be this, as
it may, at this time we should expect that 10–20% of hyponatraemic patients will not respond to vaptan.

**Do all responders respond equally well?**

It has been observed in the vaptan studies performed to date that SIADH responds best and cirrhosis worst to a given dose of vaptan in terms of aquarexia and hyponatraemia correction. The causes for these differences have not been studied in patients. However, animal models of ‘hypervolaemic’ entities (cardiac failure, liver cirrhosis) suggest that proximal tubular fluid reabsorption is increased resulting in a reduced ‘distal delivery’ of tubular fluid. Consequently, the amount of substrate available for the water transport mechanism in the ADH-driven collecting duct is diminished, as is the effectiveness of vaptans. Clinical work will tell in the future if this proposal will hold. In the meantime, the clinician will have to consider that vaptan treatment should be given in an individualized manner; the same standard dose will not serve all comers equally well. It may be too much for SIADH and too little for cirrhosis, that is for their hyponatraemia.

**Are vaptans suitable agents for emergency hyponatraemia?**

This question cannot be answered at the present time since it was never studied. However, a recent publication indicated [10] that severe acute hyponatraemia (<118 mmol/L) might become an indication for vaptan treatment. The publication gave two reasons: (1) greater ease in terms of titrating the correction rate of a hyponatraemia with a vaptan rather than with hypertonic saline and (2) no risk of pulmonary oedema. Weight loss has not been reported [12].

**Should we use vaptans to treat diuretic resistant oedema?**

Physiologists would argue that oedema is primarily a consequence of salt (and not water) retention; hence, the potential use of an aquaretic agent would appear doubtful. Indeed, even severe cases of SIADH do not show oedema. Nonetheless, industry and researchers have reported trials probing this area. (Note that in these trials the end point was not an improvement of hyponatraemia in cardiac failure or cirrhosis but reduction of oedema.) The results have not been impressive. For instance, in a trial termed EVEREST [11] (n = 4133, all of whom were in NYHA classes III and IV, mostly normonatraemic) the extra weight loss due to tolvaptan, 30 mg q.d.—an admittedly miserly dose—was ∼0.5 kg at Weeks 1, 16 and 56 of treatment. It is, however, possible that increased drinking due to thirst and dry mouth reported frequently in the tolvaptan-receiving patients prevented a more clear-cut decrease in the weight. Comparable strategies have also been proposed [12] or are currently being considered in cirrhosis with ascites and peripheral oedema. Weight loss has not been reported [12].

**Do vaptans save lives in severe cardiac failure?**

Because of suggestive evidence from a *post hoc* analysis of a subgroup of patients in a tolvaptan study called ‘ACTIV’, the question was asked whether vasopressin antagonist would lower mortality in severe cardiac failure. Given that cardiac failure is now known to be a state of neurohormonal activation (SNS, RAA system, vasopressin) plus the recognition that inhibition of at least some ‘neurohormones’ improved mortality in severe cardiac failure (β-blockers; ACEI), this was not as outrageous a concept as it may sound. However, a trial in 4133 patients (‘EVEREST’; 11) testing exactly this proposal with tolvaptan was clearly unable to show an effect in terms of improved mortality.

Does this disprove the validity of the concept? It is the bias of the present authors that it does not; we happen to believe that the EVEREST study might have been done with the wrong antagonist. V2 receptor antagonists like tolvaptan have been shown to increase the plasma vasopressin concentration 2- to 3-fold. Because with a pure V2 antagonist the ‘vascular’ V1 (vasopressin) receptor remains unblocked, V1 effects may increase as dictated by the plasma vasopressin concentration. V1 effects in the cardiovascular system have been described (a) as increased peripheral resistance; (b) as increased cardiac remodelling; (c) as stimulation of myocyte proliferation, etc.—all of which being effects that conceivably might have a role in NYHA III/IV and hence the mortality of such patients. We therefore believe that mortality indeed continues to be a very interesting issue in NYHA III/IV cardiac failure with respect to vasopressin; however, we propose that it ought to be studied with a vaptan that has V1 antagonistic properties or perhaps also with a V1/V2 mixed antagonist.

**Why do vaptans increase thirst?**

This question sounds easy. Since V2 vaptans increase the plasma osmolality, increased thirstiness appears to be a straight consequence especially in patients with a reset osmostat. However, the thirst reported by some of the patients on V2 vaptans appears to be out of proportion to the prevailing plasma osmolality (which is usually in the low or normal range, but not elevated). G. Decaux, Brussels, did not observe an increased sensation of thirst when he corrected hyponatraemia using urea (personal communication, 2008). Sometimes, patients being placed on a V2 vaptan experience a sensation of thirst and dry mouth even before they start to have more urine flow. These anecdotal observations are perplexing. If confirmed by others: is there some detail of the receptor outfit of hypothalamic osmosensitive ‘thirst-cells’ that we do not know yet, such as a V1 receptor or an additional vasopressin receptor?

**Miscellaneous**

Based on the experimental literature primarily from the laboratory of L. Bankir, Paris, studies in humans have
also been initiated to investigate whether albuminuria and proteinuria of diabetic nephropathy may be decreased after vaptan (V1/V2 mixed) treatment. To the best of our knowledge, no results of these tests have been published yet.

A frequently asked question is whether V2 vaptans increase bleeding, since DDAVP is infused to decrease bleeding in patients with von Willebrandt’s disease. Increased bleeding has not been reported in the studies conducted so far. Conivaptan, a combined V1/V2 receptor antagonist is contraindicated in liver cirrhosis; it is expected that blockade of the V1 receptor would increase flow through esophageal varices and hence might cause variceal bleeding. Recently, one laboratory has proposed that sodium sequestration into soft tissues plays a role in the regulation of extracellular sodium [13]. At this time there is no evidence that such a process has a role in hyponatraemia or in the effects of vaptans.

In summary, stay tuned! More (interesting) information about the vaptans is about to emerge in the near future.

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References


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Translation of basic science into clinical medicine: novel targets for diabetic nephropathy

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Despite major therapeutic advances, the incidence of diabetic nephropathy remains worrisome. Classical factors contributing to its pathology (e.g. hypertension, hyperglycaemia, hyperinsulinaemia, and hyperlipidaemia) are now amenable to treatment, but current therapies do not fully prevent renal complications. The experimental study of animals has recently incriminated newer culprits, such as hypoxia, oxidative stress, advanced glycation, etc. and identified several target molecules. These progresses remain to be translated into clinical medicine.