

## To test, or not to test, and how ... copeptin, please advise!

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Fluid homeostasis is maintained by thirst sensation, liquid intake, cardiac and kidney function, insensible water losses and renal solute excretion. In this complex interplay, the antidiuretic hormone vasopressin (AVP) plays a pivotal role by regulating urine output, promoting free water reabsorption through aquaporin “water channel” molecules expressed in renal collecting duct cells. Various stimuli, most importantly hyperosmolality and hypovolaemia, but also stress signals such as nausea or pain, promote AVP release into the bloodstream. Besides regulating antidiuresis, AVP is a stimulator of adrenocorticotrophic hormone (ACTH) secretion and thus has an important part in the activation of the hypothalamic-pituitary-adrenal (HPA) axis. It is relevant to consider this role of AVP as a stress hormone when testing the antidiuretic system, as AVP levels are influenced by situational stress levels, irrespective of the osmotic and volume status.

Both insufficient AVP concentrations and inadequate response of the target organ will cause diabetes insipidus (“tasteless water flow”), a heterogeneous disorder characterised by pathological quantities of hypotonic urine (polyuria) and – if the thirst mechanism is intact – excessive thirst (polydipsia). Hypotonic polyuria is also present in primary polydipsia, where AVP secretion is physiologically suppressed owing to abnormally large fluid intake.

The differential diagnosis of the polyuria-polydipsia syndrome is notoriously cumbersome. After excluding pollakiuria and solute diuresis (typically due to glycosuria), we are often faced with the question of whether to subject the patient to a troublesome and potentially dangerous stimulatory testing procedure, usually some modified form of the indirect water deprivation test [1]. By withholding all fluids for hours and, if necessary, administering hypertonic saline in order to sufficiently stimulate AVP synthesis and secretion, the renal capacity to concentrate urine before and after the administration of synthetic AVP is assessed, aiming to differentiate between neurogenic or renal diabetes insipidus and primary polydipsia.

Unfortunately, however, test results are often ambiguous, not least due to “washout” of the corticomedullary osmogradients as a consequence of prolonged high renal fluid throughput of any cause, making it impossible to reliably distinguish between partial forms of diabetes insipidus and primary polydipsia. Dependable AVP assays were a big

step forward in establishing a more accurate, “direct” test [2]. However, published AVP ranges for the various forms of diabetes insipidus still overlap; and reliable assays, tedious and time consuming as they are, never found their way into clinical routine.

The introduction of a routine-proof sandwich immunoluminometric assay for copeptin, the biochemically stable C-terminal glycopeptide segment of the AVP prohormone [3], paved the way out of this stalemate. Since it derives from the same precursor molecule and co-localises in the same secretory granules, copeptin is stoichiometrically released with AVP from the posterior pituitary, representing a sound surrogate marker over a broad range of osmolalities [4].

Based on these concepts, Mirjam Christ-Crain and her group systematically renovated the diagnostic approach to polyuria-polydipsia syndrome, now reviewed in *Swiss Medical Weekly* [5]. In a series of prospective studies, they first established copeptin reference values to distinguish between neurogenic diabetes insipidus, nephrogenic diabetes insipidus and primary polydipsia with high accuracy, using baseline and stimulated copeptin values in a combined water deprivation-hypertonic saline infusion test. They then went on to demonstrate that measurement of copeptin stimulated by hypertonic saline infusion, but without prior thirsting, provided better diagnostic accuracy than the indirect water deprivation test in differentiating central diabetes insipidus from primary polydipsia. Most recently, they utilised arginine infusion (a test that is traditionally used to evaluate growth hormone secretory capacity) to stimulate the posterior pituitary. Again, they could demonstrate a high diagnostic accuracy in differentiating neurogenic diabetes insipidus from primary polydipsia.

This work not so much adds to our understanding of the antidiuretic mechanism as helps overcome the serious limitations of the previously published tests. Although methodologically hampered by the inherent lack of a diagnostic gold standard, the studies by Mirjam Christ-Crain and co-workers were carefully conducted and included many more patients than all previous landmark papers. They tell us when it is not necessary to stimulate the neurohypophysis, and if it is, how best to do it. They facilitate solid therapeutic decisions, which is particularly relevant since converse treatment strategies are needed in primary polyuria

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and other forms of diabetes insipidus; thus, a correct diagnosis is key to avoid hazards for the patient. The arginine infusion test may well prove feasible for office use, since potentially dangerous hypernatraemia is avoided – another valuable gain in patient safety. And last but not least, patients will be grateful for no longer having to thirst for hours, only to be told afterward that their diagnosis is still unclear.

#### Disclosure statement

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