



Thermo Scientific
B·R·A·H·M·S Copeptin proAVP

Fast, precise, and smart

Copeptin – the better vasopressin

Achieving the full diagnostic potential of vasopressin with its stable surrogate Copeptin • Optimizing differential diagnosis of endocrine diseases • Improving patient management and lab workflow

Thermo
SCIENTIFIC

Achieve new diagnostic possibilities

with the vasopressin surrogate Copeptin

Vasopressin biology

Vasopressin (AVP), also known as antidiuretic hormone (ADH), has two primary functions: to retain water in the body and to constrict blood vessels. It is implicated in a variety of diseases and conditions and is of great diagnostic value (Figure 2).

However, in clinical routine, vasopressin is rarely measured because of technical difficulties and limited reliability of available assays. Therefore vasopressin measurement is not adequately implemented in diagnostic strategies.

The vasopressin surrogate Copeptin now opens the possibility to take full advantage of the hormone's diagnostic potential:

- **significant correlation with vasopressin**
- **extreme stability *ex vivo***
- **easy and precise measurement**
- **results within 1 hour**

Vasopressin synthesis and release

Vasopressin (AVP) is a small neurohypophysial hormone that is synthesized in the hypothalamus and stored in secretory granules in the posterior pituitary gland. It is made as part of a larger precursor molecule (pre-provasopressin) which is cleaved during processing. Cleavage leads to release of individual peptides vasopressin, neurophysin II and Copeptin (CT-proAVP) in equimolar amounts (*i.e.*, 1:1 ratio) (Figure 1).⁸

The main stimuli for vasopressin release from its storage granules are increased plasma osmolality and decreased blood volume, as for example in hemodynamic changes.¹⁶

After release into the bloodstream, vasopressin can exert its anti-diuretic and vasoconstrictive actions via V2 (kidney) and V1 (vasculature) receptors respectively.⁸

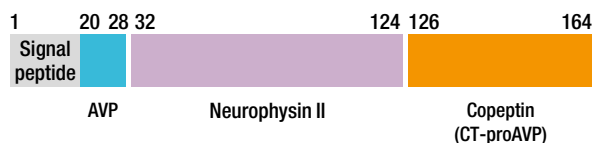


Figure 1 Pre-provasopressin molecule, consisting of a signal peptide, vasopressin (AVP), neurophysin II and Copeptin (CT-proAVP) (numbers: amino acids)¹⁵

Copeptin can be used as a surrogate for vasopressin

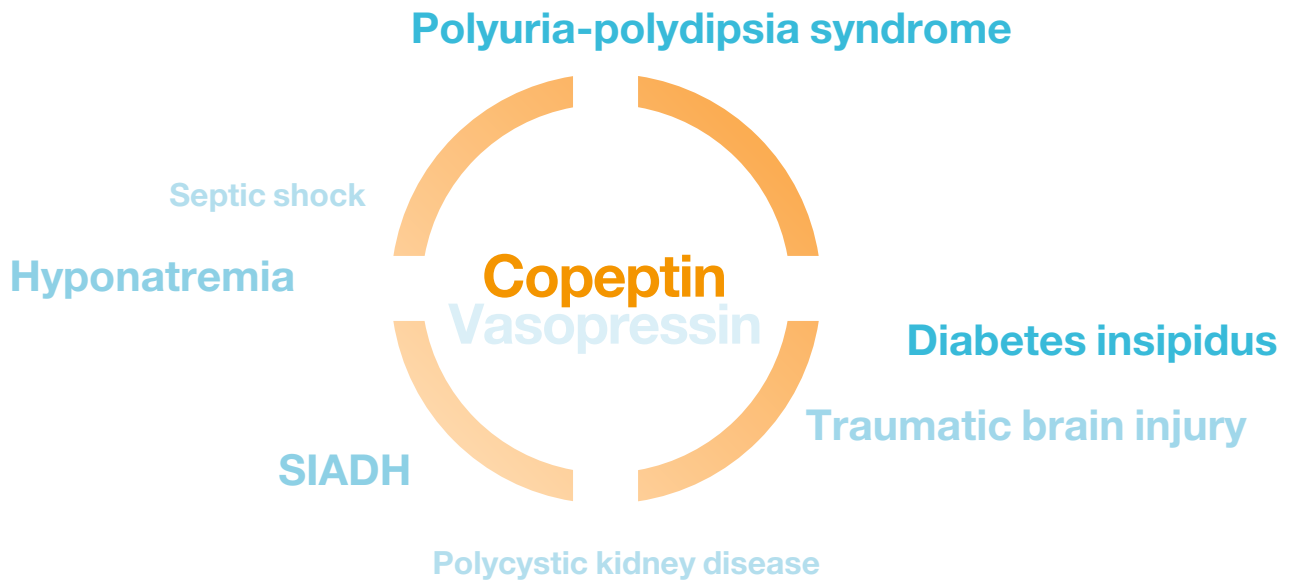


Figure 2 Vasopressin-related conditions

Copeptin and vasopressin derive 1:1 from the same precursor

Copeptin (CT-proAVP) forms the C-terminal part of pre-provasopressin (Figure 1) and is suggested to have an important function in correct vasopressin folding.¹⁷ Upon stimulation, vasopressin and Copeptin are released from their storage granules and rapidly enter the bloodstream in equimolar amounts (1:1 ratio).^{9,10} **Across a variety of clinical settings, Copeptin and vasopressin levels have consistently been shown to significantly correlate** (Figure 3).^{11,12,13}

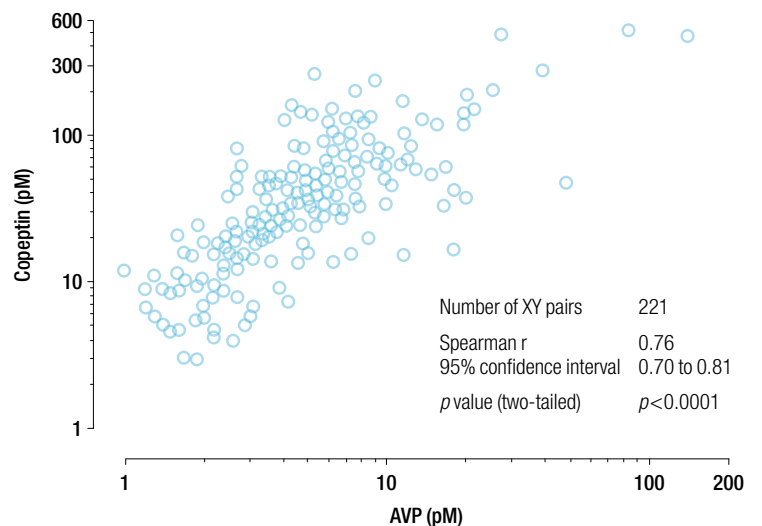


Figure 3 Correlation between plasma vasopressin and Copeptin concentrations in non-cardiac surgery patients (n=41)¹³

Copeptin – same kinetics as vasopressin

but extremely stable

Copeptin responds equally to vasopressin stimuli

The main stimuli for vasopressin release from its storage granules are increased plasma osmolality and decreased blood volume.

Copeptin and vasopressin respond equally to changes in blood volume¹⁶ and correlate strongly with changes in plasma osmolality over a wide range (Figure 4 and Table 1).¹

Compared to vasopressin, Copeptin correlates better with plasma osmolality

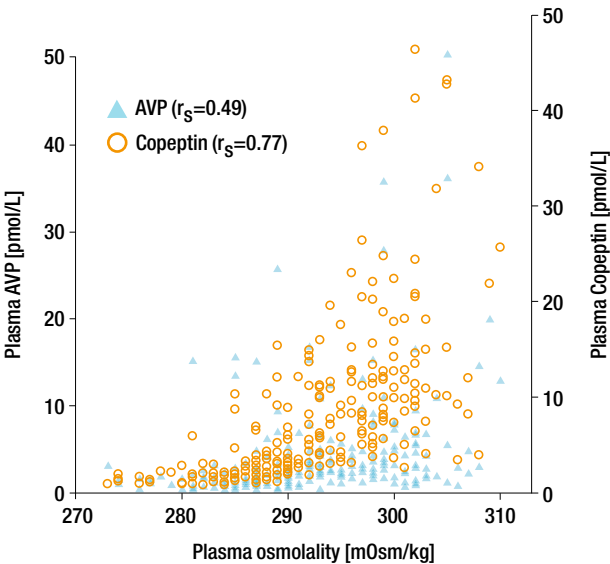


Figure 4 Plasma vasopressin and Copeptin concentrations measured during individual water load and saline infusion tests; r_s refers to Spearman’s rank correlation coefficient (adapted from ¹). The substantially higher r_s of Copeptin indicates that this biomarker much more closely correlates with osmolality than does vasopressin.

Osmolality [mmol/kg]	Vasopressin [pmol/L]	Copeptin [pmol/L]
270-280	<1.4	0.81-11.6
281-285	<2.3	1.0-13.7
286-290	0.9-4.6	1.5-15.3
291-295	1.9-6.5	2.3-24.5
296-300	3.7-11.1	2.4-28.2

Table 1 Vasopressin²² and Copeptin^{1, 5, 21} values in relation to plasma osmolality



Copeptin: stable ex vivo for several days

Because of technical limitations of AVP assays, vasopressin concentrations were rarely measured in the past. Hence, vasopressin cut-offs were not implemented in diagnostic strategies. In contrast to vasopressin, Copeptin is stable at room temperature for several days (Figure 5). This extraordinary stability facilitates clinical sample handling and logistics, increasing the sensitivity and reliability of results.

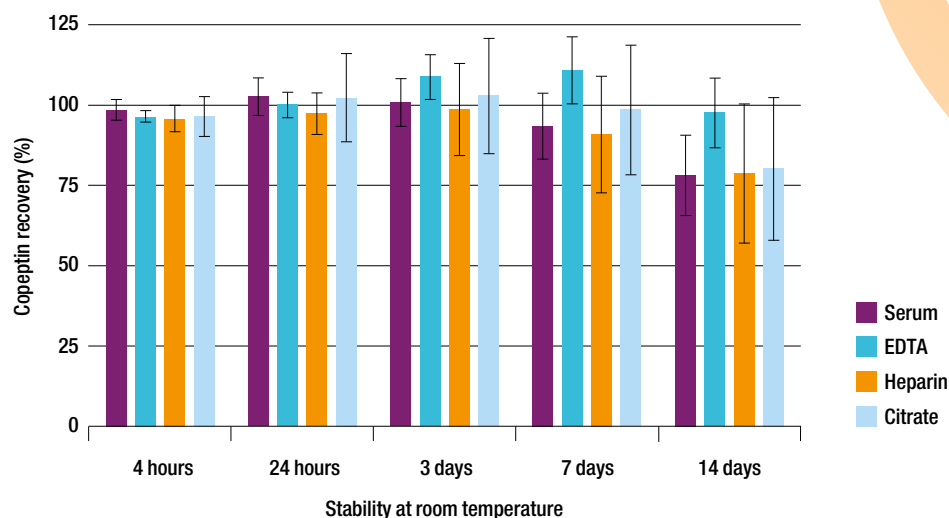


Figure 5 Stability of Copeptin over time in various matrices at room temperature. Measurements after the indicated intervals are expressed as percentages of the initial measurement (n=5) ¹⁵

*Thermo Scientific
B·R·A·H·M·S Copeptin
proAVP assays reliably replace
the measurement of highly
unstable vasopressin and open
the possibility to achieve the
full diagnostic potential of this
hormone.*

The extraordinary stability
of Copeptin eases lab logistics

Copeptin advantages for lab and clinic

Easy handling – precise results

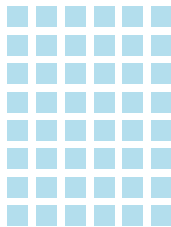
Fastest time to result

In the past, vasopressin measurements have not been routinely used in the laboratory or clinic. This is mainly due to demanding sample handling requirements (*i.e.*, complex specimen preparation; at least -20° C storage) and technically limited assay performance (long incubation steps; radioactive labeling) which were labor-intensive, time-consuming and error-prone.

The manual Thermo Scientific™ B·R·A·H·M·S™ CT-proAVP LIA and the automated Thermo Scientific™ B·R·A·H·M·S™ Copeptin proAVP KRYPTOR™ assays are easy-to-handle, reliable alternatives allowing fast, precise measurement of the vasopressin surrogate Copeptin (CT-proAVP). With either assay format, time to result is under 3 hours, so that results can be delivered the very same day. For the first time, convenient, robust and rapid vasopressin monitoring is available in everyday practice.

Easy handling and short incubation time allow delivery of results to clinicians the same day

48 hours



2 hours

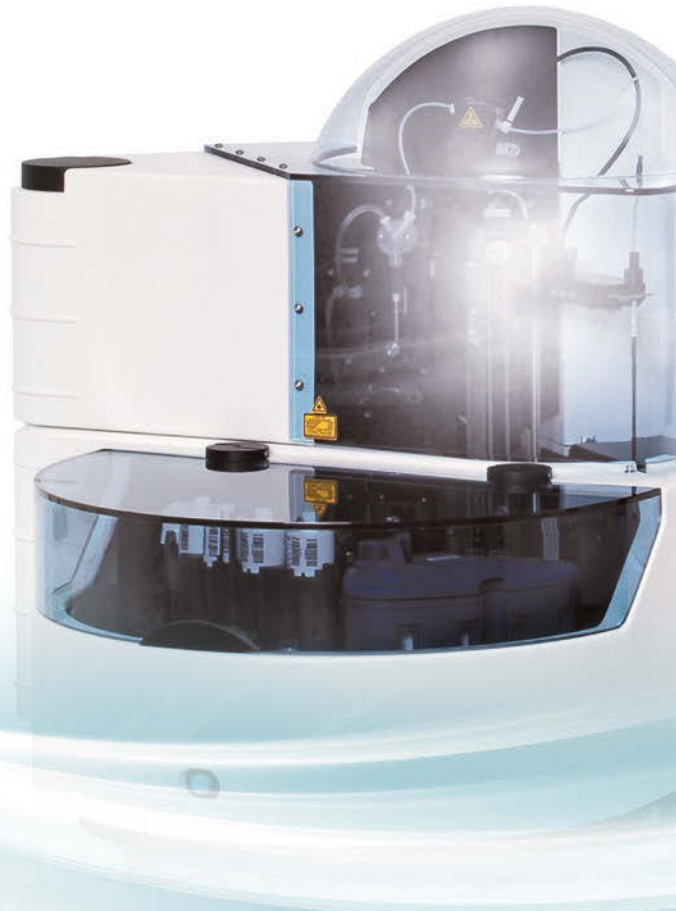


<1 hour



Competitor vasopressin RIA	CT-proAVP LIA	Copeptin proAVP KRYPTOR
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Figure 6 Incubation times of Thermo Scientific B·R·A·H·M·S CT-proAVP LIA and Copeptin proAVP KRYPTOR assays are significantly shorter than those of commercial vasopressin assays⁷





Superior precision

KRYPTOR provides exceptional intra- and inter-assay precision due to homogeneous assay design without any washing or separation steps.

Measurement of Copeptin as a surrogate for vasopressin is less error-prone because of the molecular advantages of Copeptin such as larger size and extraordinary *ex vivo* stability.

Features	Vasopressin limitations	Copeptin (CT-proAVP) advantages
Ex vivo stability	instable even when stored at -20 °C	>3 days at room temperature
Sample volume	400 µL	50 µL
Matrix	Plasma (EDTA)	Serum & plasma (EDTA, heparin)
Time to result	3 working days	14 min
Handling	manual	automated
Sensitivity	low (because of small molecule size, measurement is only possible by competitive immunoassays)	high (due to its larger size, Copeptin can be measured using a sensitive sandwich immunoassay)
Measuring range	1.25-80 pg/mL (= 1.15-73.8 pmol/L)	0.7 - 500 pmol/L (up to 2000 pmol/L with automatic dilution)

Table 2 Comparison of a commercially available vasopressin radioimmunoassay³ with the Thermo Scientific B-R-A-H-M-S Copeptin proAVP KRYPTOR assay



Exceptionally precise, fast and easy

Thermo Scientific B-R-A-H-M-S KRYPTOR compact PLUS

Article number: 106172

Clinical use of Copeptin

in efficiently assessing water balance disorders

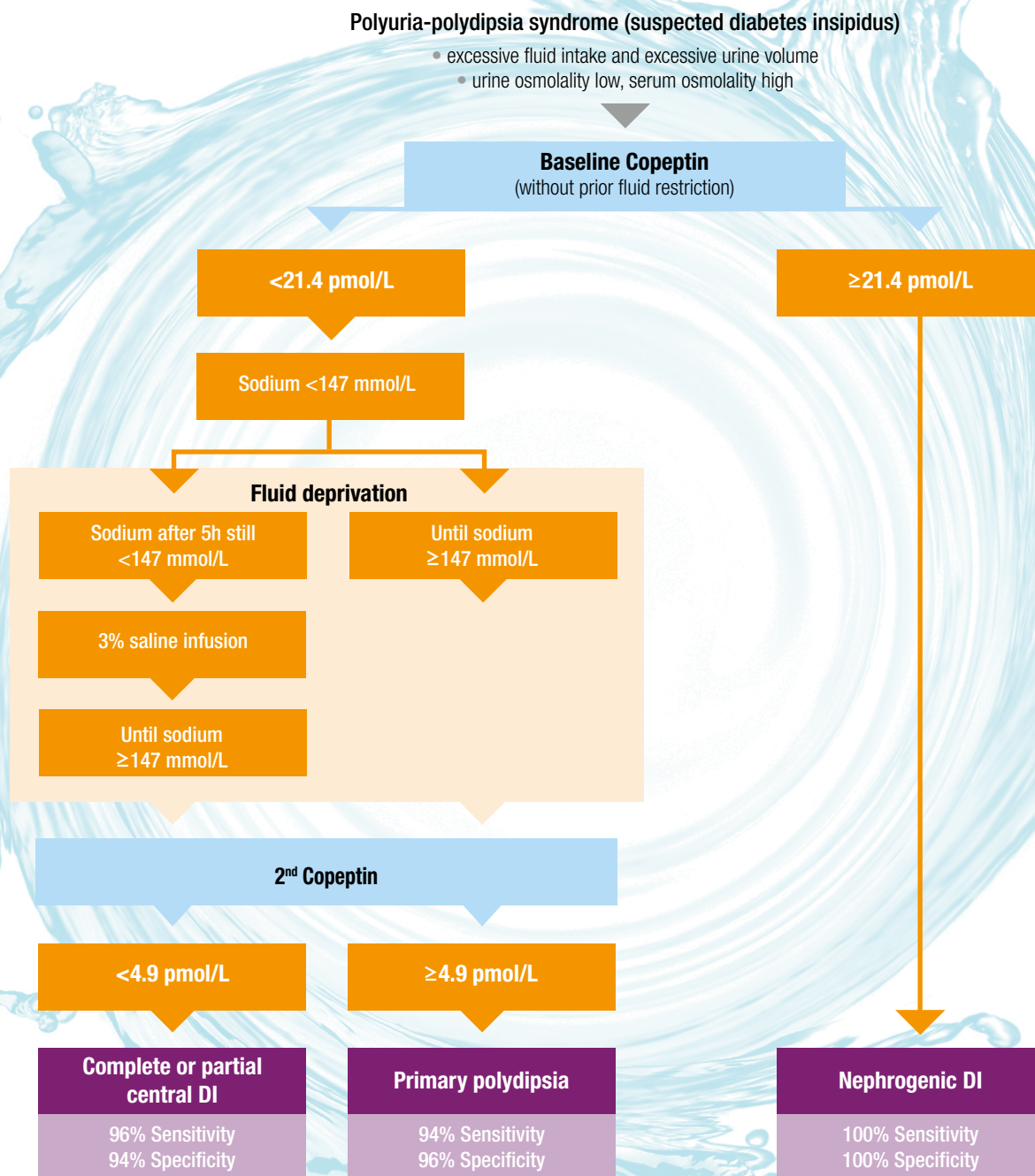


Figure 7 Algorithm for differential diagnosis of polyuria-polydipsia syndrome using Copeptin in patients with suspected diabetes insipidus (adapted from²³)



successful
in clinical routine

Polyuria-polydipsia syndrome: improved differential diagnosis

The challenge in the diagnosis of the polyuria-polydipsia syndrome is differentiating between cases of primary polydipsia and diabetes insipidus.

The diagnostic method of choice would be direct vasopressin determination, but the molecular characteristics of vasopressin make such measurement very complex and error-prone, hence unreliable. Consequently, "direct vasopressin testing" has not been established as a diagnostic routine.

Now, a single Copeptin measurement can immediately distinguish central diabetes insipidus from nephrogenic diabetes insipidus (Figure 7).

Thus Copeptin measurement reduces the burden of the water deprivation test for the majority of patients and improves patient management within the clinic.^{5,24}

Pituitary surgery: easy monitoring for vasopressin deficiency

Pituitary tumors can cause various hormone deficiencies and water metabolism disorders due to their unique site. Remarkably, after pituitary surgery, diabetes insipidus is observed in 18.5% of patients and hyponatremia in 9%-24%.

Therefore, during recovery from pituitary surgery, patients should be closely monitored for possible hormone deficiencies including lack of vasopressin during the postoperative recovery phase (Figure 8).⁴

Traumatic brain injury: reliable follow-up for hypopituitarism

Neurohypophyseal dysfunction is common following moderate to severe brain injury. Diabetes insipidus can occur in up to 26% of traumatic brain injury victims in the acute phase, as can hyponatremia as a consequence of SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion).⁶

Recent pilot studies suggest a potential value of Copeptin in following patients with traumatic brain injury.

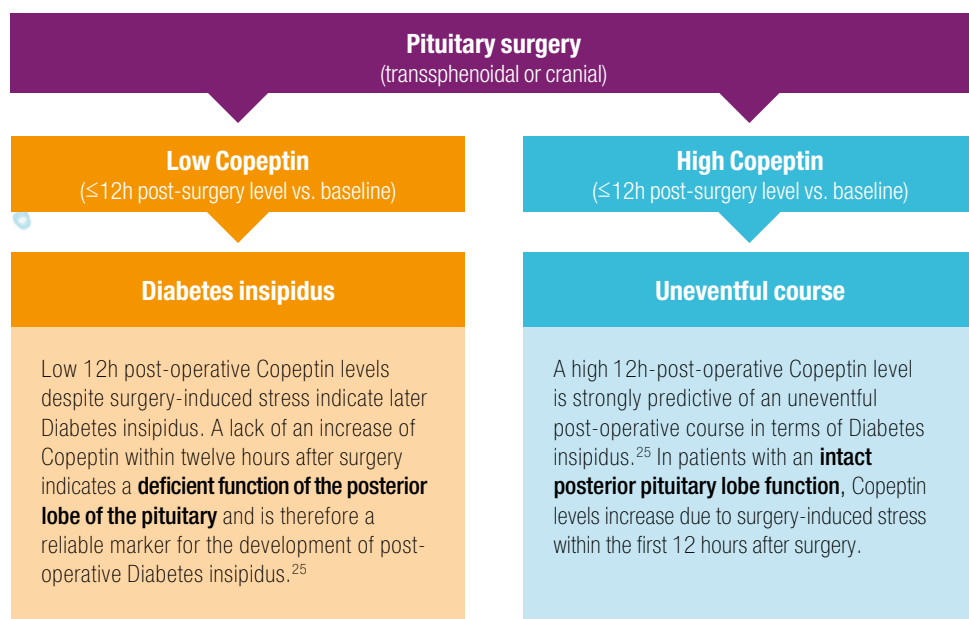


Figure 8 Benefit of using Copeptin in the follow-up of pituitary surgery (adapted from ²⁵)

Unresolved diagnostic challenges – the future of Copeptin testing

Hyponatremia: new possibilities for differential diagnostics?

Hyponatremia is defined as plasma sodium concentrations below 135 mmol/L, which usually imply an excess of water relative to sodium. Hyponatremia therefore primarily reflects a disturbance in water balance rather than too little sodium. Since hyponatremia occurs as a common symptom in a variety of disorders (such as *e.g.* SIADH, heart failure) requiring different treatments, convenient diagnostic parameters are needed in order to guide treatment strategy.¹⁸

In this regard, Copeptin is a promising biomarker because an osmotically inappropriate vasopressin secretion is considered to be the predominant mechanism in most hyponatremic states.

Polycystic kidney diseases: better assessment of disease progression and management

Experimental evidence shows that vasopressin plays a detrimental role in the initiation and progression of polycystic kidney disease (PKD), the most common hereditary renal disorder.²⁴

A first set of clinical studies examined the role of vasopressin in the course of autosomal dominant polycystic kidney disease (ADPKD) by using Copeptin as a vasopressin surrogate marker. **Copeptin levels were shown to correlate positively with ADPKD severity and negatively with the glomerular filtration rate (GFR).** These results are in accordance with studies in which vasopressin antagonists had a renoprotective effect in ADPKD, suggesting a role for vasopressin in disease progression.¹⁴



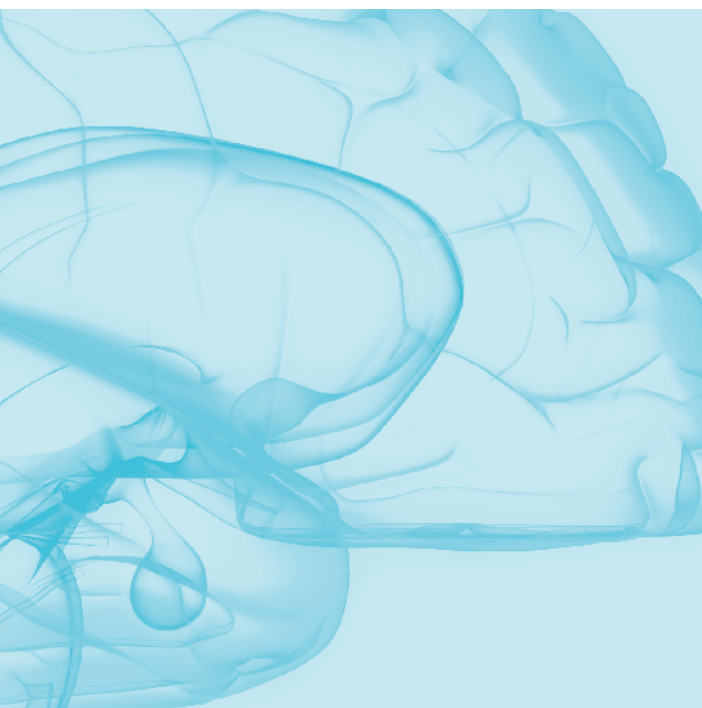


Septic shock: fine-tuning of exogenous vasopressin therapy

In septic shock, relative vasopressin deficiency has been reported.²⁰ After an initial rise of circulating vasopressin, vasopressin levels fall significantly within hours without returning to basal values. This phenomenon might be due to depletion of stored vasopressin as well as inhibition of new vasopressin synthesis and release within the hypothalamus and pituitary.¹⁹

Combined norepinephrine/vasopressin usage is considered to substantially improve patient management in this life-threatening condition. However, in the past, it has been difficult to refine dosing schemes, impairing treatment efficacy.⁷

Hence, determination of endogenous vasopressin levels by measuring Copeptin might be a promising tool to optimize care for patients with severe sepsis or septic shock.



"In conclusion, after several decades of minimal interest, vasopressin has become a hot topic in the past few years. More attention should now be given to the vasopressin-thirst-urine concentration axis in patient care. Vasopressin and/or copeptin should be measured in new cohorts and clinical investigations."



Your options to replace vasopressin (AVP) assays with easy and precise Copeptin (CT-proAVP) assays

	B-R-A-H-M-S Copeptin proAVP KRYPTOR	B-R-A-H-M-S CT-proAVP LIA
Assay format	Automated immunofluorescent assay (KRYPTOR)	Immunoluminometric assay (ILMA)
Technology	Time Resolved Amplified Cryptate Emission (TRACE)	One-step assay with coated-tube technology
Direct measurement	0.7...500 pmol/L	0.4...1250 pmol/L
Measuring range with automatic dilution	0.7...2000 pmol/L	
Functional assay sensitivity (FAS)	<1,08 pmol/L	<1 pmol/L
Detection limit	0.69 pmol/L	0.4 pmol/L
Incubation time	14 minutes	2 hours
Sample volume	50 µL	50 µL
Sample type	Serum, plasma (EDTA, heparin)	Serum, plasma
Determinations	50	50 100
Article number	857.050	119.050 119.100

References

1. Balanescu S et al., J Clin Endocrinol Metab 2011; 96(4): 1046-52
2. Bankir L et al., Nat Rev Nephrol 2013; 9(4): 223-39
3. Bühlman Vasopressin RIA (RK-VPD), Instructions for Use
4. Devin JK et al., Neurosurg Clin N Am 2012; 23: 679-89
5. Fenske W et al., J Clin Endocrinol Metab 2011; 96(5): 1506-15
6. Glynn N, Clin Endocrinol 2013; 78(1): 17-20
7. Gordon AC, JICS 2011; 12(1): 11-14
8. Holt NF et al., J Cardiothorac Vasc Anesth 2010; 24(2): 330-47
9. Holwerda DA, Eur J Biochem 1972; 28(3): 334-9
10. Holwerda DA, Eur J Biochem 1972; 28(3): 340-6
11. Jochberger S et al., Anaesth Intensive Care 2006; 34(4): 498-500
12. Jochberger S et al., Intensive Care Med 2009; 35(3): 489-97
13. Jochberger S et al., Shock 2009; 31(2): 132-8
14. Meijer E et al., Clin J Am Soc Nephrol 2011; 6(2): 361-8
15. Morgenthaler NG et al., Clin Chem 2006; 52(1): 112-9
16. Morgenthaler NG et al., Shock 2007; 28(2): 219-26
17. Repaske DR et al., J Clin Endocrinol Metab 1997; 82: 51-6
18. Schrier RW, J Am Soc Nephrol 2006; 17: 1820-32
19. Sharshar T et al., Crit Care Med 2002; 30(3): 497-500
20. Sharshar T et al., Crit Care Med 2003; 31(6): 1752-8
21. Szinnai G et al., J Clin Endocrinol Metab 2007; 92(10): 3973-8
22. Thomas L, Clinical Laboratory Diagnostics, 1st English Edition, Chapter 8.5 (pp. 302-306), TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, Germany
23. Timper K et al., J Clin Endocrinol Metab 2015; 100(6): 2268-74
24. Wang X et al., J Am Soc Nephrol 2008; 19(1): 102-8
25. Winzeler B et al., J Clin Endocrinol Metab 2015; 100(6): 2275-82

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