Physiological area of normality of copeptin in normal- to hyperosmolar states

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Objectives

Background:
- Copeptin is the C-terminal portion of the precursor of vasopressin and secreted in an equimolar ratio.
- In contrast to vasopressin, copeptin is stable in vitro and easy and more reliable to measure.
- Miscellaneous studies investigated both peptides describing similar kinetics.
- Data describing the physiological area of normality of copeptin over the entire osmotic range as well as the definition of the half-life time of copeptin.

Aim of the study:
- To evaluate the physiological area of normality of copeptin in normal- to hyperosmolar states.
- To define the half-life time of copeptin.

Study participants:
- Healthy subjects matched for different age (20 to 54 years) and gender fulfilling all inclusion criteria were recruited by public insertion.
- Recruitment centers: University Hospital of Basel and University Hospital of Würzburg.
- Recruitment period: September 2012 until September 2014.

Trial flow (baseline, phase 1, 2 & 3):
- Preliminary medical evaluation including medical history, clinical items (e.g. heart rate, blood pressure) and baseline laboratory.
- Phase 1: Administration of hypertonic saline infusion (3% saline, 513mmol/L) at a given rate (0.15ml/kg body weight for a bolus of 250ml within the first 15 minutes) until a serum sodium level of at least 150mmol/L is reached.
- Phase 2: Oral water load (30ml/kg body weight) within 30 minutes.
- Phase 3: Infusion of glucose 5% over 40-60 minutes until plasma sodium reached the approx. initial value.
- Close meshed laboratory (i.e. plasma copeptin, sodium and osmolality) and clinical controls during all three phases.

Methods

Results

Characteristics Study subjects (n=16)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study subjects (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female: 9 (56%)</td>
</tr>
<tr>
<td>Clinical variables</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Age distribution, y</td>
<td>27 (25, 34.5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.72 (21.2, 24.4)</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>122 (114, 129)</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>74 (69, 80)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68 (65, 71)</td>
</tr>
<tr>
<td>Laboratory variables</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>139 (136, 141)</td>
</tr>
<tr>
<td>Serum copeptin, pmol/L</td>
<td>4 (3.1, 6)</td>
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<tr>
<td>Serum osmolality, mmol/L</td>
<td>289 (281, 296)</td>
</tr>
<tr>
<td>Urine osmolality, mmol/L</td>
<td>668 (593, 802)</td>
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Table 1: Baseline characteristics study participants.

The trial was performed in 91 healthy humans in an ambulatory setting. The baseline characteristics of the study subjects are shown in Table 1. All study participants had uneventful medical histories and normal findings on baseline laboratory and physical examination. Upon hypertonic saline infusion plasma sodium levels increased from a median of 139mmol/L (SD 2.2) to 152mmol/L (SD 2.52), plasma osmolality from 289mosmol/kg (SD 9.1) to 311mosmol/kg (SD 8.21) and plasma copeptin from 4pmol/L (SD 3.8) to 32.9pmol/L (SD 28.7). The maximal value of copeptin was reached after 140 minutes (SD 29.1), without a time lag to the maximum of plasma sodium or osmolality (reached after 145 SD 32.6) and 149 SD 30.5 minutes, respectively. There was a moderate to strong positive correlation between plasma copeptin and plasma sodium (r=0.57, p<0.05) and plasma copeptin and plasma osmolality (r=0.53, p<0.05).

The area of normality in phase 1 (Figure 1) was calculated by population modeling with the Hill function for individual profiles. Using population parameter and interindividual variability estimates, 1000 populations were simulated and the area of normality was calculated based on 5th to 95th percentiles of the simulated data.

As soon as hypertonic saline infusion (phase 1) was stopped and oral water load (phase 2) was performed, copeptin-values decreased. Any stimulus for copeptin had vanished once the glucose 5% infusion (phase 3) was started. Copeptin half-life time was calculated based on phase 3 data with the mono-exponential decay approach resulting in 82min.

In Figure 2 the shaded area is delimited by 5th to 95th percentiles of measured data. The black line indicates the lowest smoothing curve.

Conclusion

There is a correlation between plasma copeptin, plasma sodium and plasma osmolality levels from normo- to hyperosmolar states. Similar to data existing for AVP the area of normality indicates that even smallest increases in osmolality and sodium levels result in a rapid increase of copeptin.

Once the major stimulus (hyperosmolality) is vanished copeptin decreases rapidly. The half-life time estimated by means of our study is 4x higher than the half-life time documented for AVP (15-20 minutes).

This is the first study providing an area under the curve for copeptin and giving information about the half-life time of copeptin.