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

Ingeborg Schnyder [a], Konrad Strauss [b], Gilbert Koch [d], Carla Walti [a], Marc Pfister [d], Bruno Allolio [b], Wiebke Fenske [c] *, Mirjam Christ-Crain [a] *

* equally contributing senior authors

Department of endocrinology Universtiy Hospital of Basel [a], University Hospital of Würzburg [b] and University Hospital of Leipzig [c]
Pediatric Pharmacology and Pharmacometrics Research Center, University Children`s Hospital of Basel [d]

## 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 are still missing

### 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

## Methods

### Study participants:

- healthy subjects matched for different age (20 to 54 years) and gender fulfilling all inclusion criteria were recruited by public insertion
- recruiting centers: University Hospital of Basel and University Hospital of Würzburg
- recruitment-period: september 2012 until september 2014

### Trialflow (baseline, phase 1, 2 & 3):

- preliminary medical evaluation including medical history, clinical items (e.g. heart rate, bloodpressure) and baseline laboratory
- **phase 1**: administration of hypertonic saline infusion (3% saline, 513mOsm/l) at a given rate (0.15ml/kg bodyweight after a bolus of 250ml within the first 15 minutes) until a serum sodium level of at least 150mmol/l is reached
- **phase 2**: oral waterload (30ml/kg bodyweight) within 30minutes
- **phase 3**: infusion of glucose 5% over 40-60minutes until plasma sodium reached the approx. initial value

| trialflow | sodium 135-145mmol/l | Phase 1 hypertonic saline infusion (3%) (0.15ml/kg BW per minute) | sodium ≥ 150mmol/l | Phase 2 waterload (30ml/kg BW) | Phase 3 Glucose 5% Infusion (approx. 500ml) | sodium 135-145mmol/l |
|---|---|---|---|---|---|---|
| duration | | until sodium >150mmol/l (Maximum 180min) | | 30min | 40-60min | |

- close meshed laboratory (i.a. plasma copeptin, -sodium and -osmolality) and clinical controlls during all three phases

## Results

| Characteristics | Study subjects (n=91) |
|---|---|
| Females, % (n) | 51.6 (47) |
| **Clinical variables** | **Median (IQR)** |
| Age distribution, y | 27 (25, 34.5) |
| BMI, kg/m² | 22.72 (21.2, 24.8) |
| Systolic blood pressure, mmHg | 122 (114, 129) |
| Diastolic blood pressure, mmHg | 74.5 (67, 82) |
| Heart rate bprm | 68 (60, 75) |
| **Laboratory variables** | **Median (IQR)** |
| Serum sodium, mmol/l | 139 (138, 141) |
| Serum copeptin, pmol/l | 4 (3.1, 6) |
| Serum osmolality, mosml/kg | 289 (281, 295) |
| Urine osmolality, mosml/kg | 686 (300, 885) |

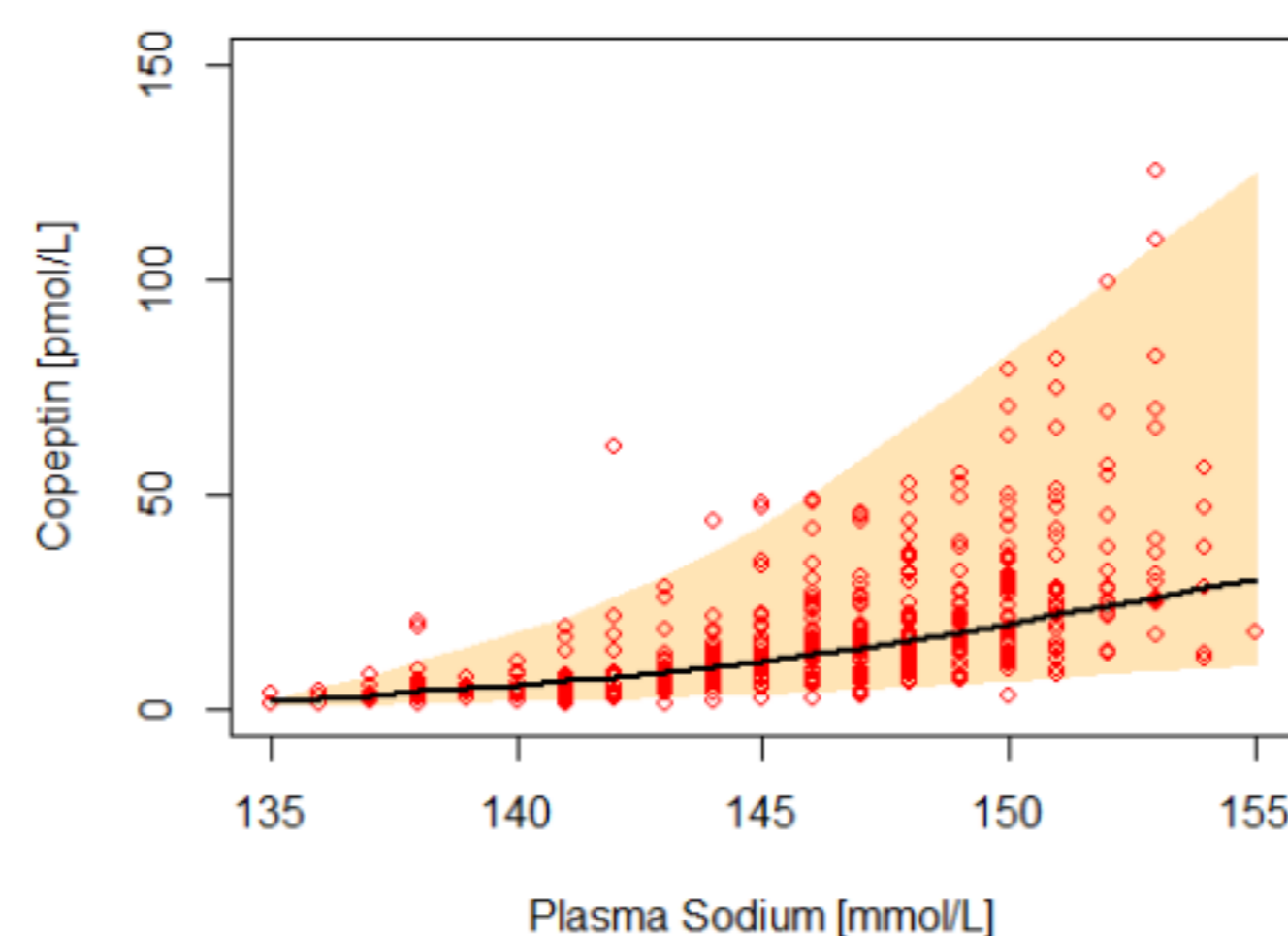Tbl. 1: Baseline characteristics study participants

Fig. 1: Physiological area of normality of copeptin in normal- to hyperosmolar states (phase 1)

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 studyparticipants had uneventful medical histories and normal findings on baseline laboratory and physical evaluation. 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 289mosml/kg (SD 9.1) to 311mosml/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 140minutes (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 modelling 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.
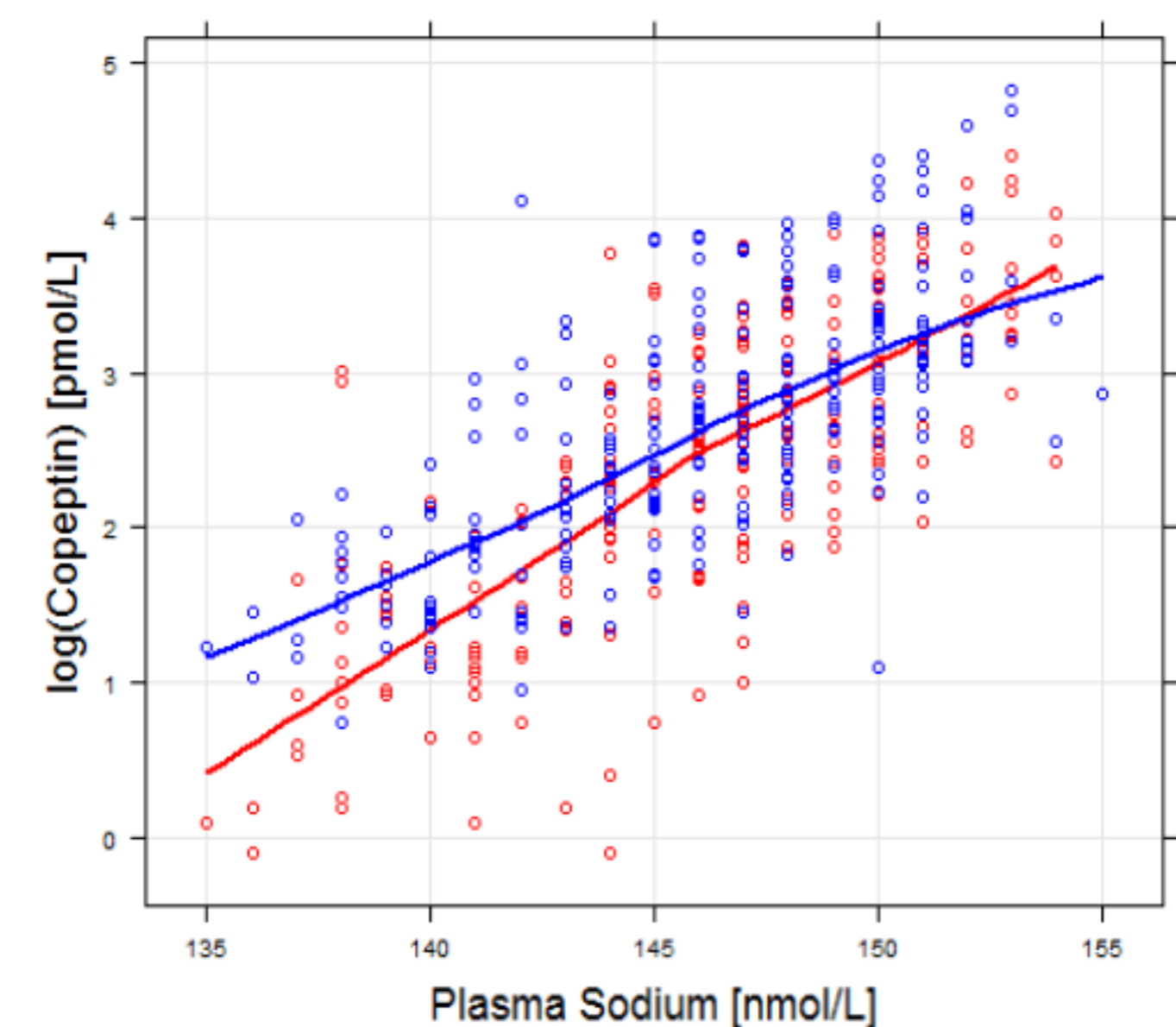
Fig. 3: Log-copeptin values (women= red dots, men=blue dots) plotted against sodium-values according to phase 1. Baseline Copeptin Median women: 3.2pmol/l (IQR 2.45, 4.4), men: 4.65pmol/l (IQR 3.9, 7), p<0.05. Max Copeptin Median women: 34.6pmol/l (IQR 19.9, 46.8), men: 28.7pmol/l (IQR 22, 39.8). Delta Median women: 31.2pmol/l, men: 23.1pmol/l, p=ns
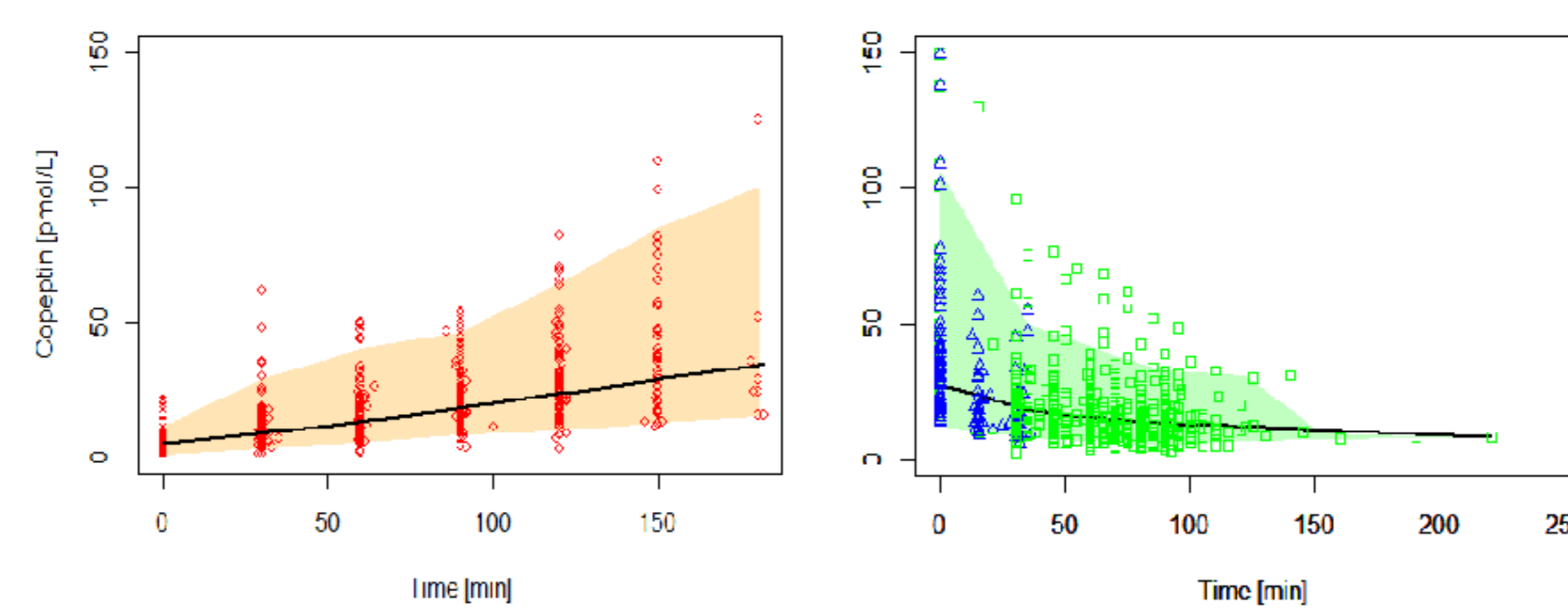
Fig. 2: Physiological area of normality of copeptin/time representing all three phases ( phase 1, phase 2, phase 3)

As soon as hypertonic saline infusion (phase 1) was stopped and oral waterload (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.

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Pituitary basic and neuroendocrinology
Ingeborg Schnyder
DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND
PosterSessionOnline.com