Model for characterizing copeptin kinetics and response in healthy subjects

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Introduction and Objectives

Introduction

Copeptin is the C-terminal portion of the precursor of vasopressin and secreted in an equimolar ratio. Vasopressin is used in clinic to diagnose diabetes insipidus. In contrast to vasopressin, copeptin is stable in vitro, and easier and more reliable to measure.

Objectives

To develop a semi-mechanistic PKPD model to characterize kinetics of copeptin and sodium related increase in central copeptin release in healthy subjects

Data and Methods

Study Participants

Data from 91 subjects from two centres (58 from USB Basel and 33 from University Hospital of Würzburg) were available.

Characteristics	Study subjects (n=91)
Females, % *(n)*	51.6 (47)
Clinical variables	**Median (IQR)**
Age distribution, *y*	27 (25, 34.5)
BMI, kg/m^2	22.72 (21.2, 24.8)
Systolic blood pressure, *mmHg*	122 (114, 129)
Disatolic blood pressure, *mmHg*	74.5 (67, 82)
Heart rate *bpm*	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)

Experimental Design

The experimental design consists of three phases:

Phase 1: Administration of hypertonic saline infusion (3% saline, 513 mOsm/l) at a given rate until a serum sodium level of at least 150 mmol/l is reached or for 180 min. Additionally, 70 subjects obtained a extra bolus saline infusion for the first 15 min of 250 ml (Basel) and 225 ml (Würzburg).

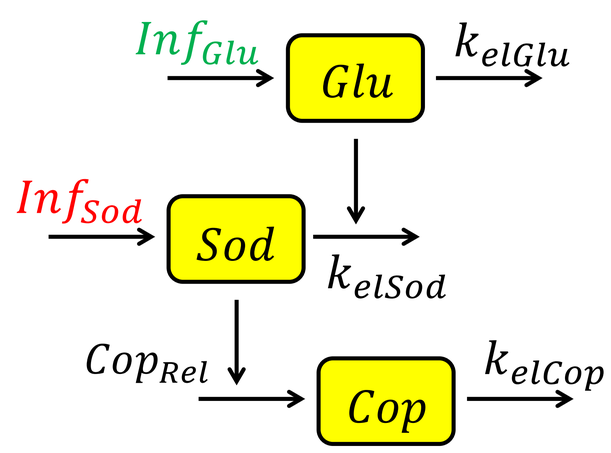
Phase 2: Oral waterload (30 ml/kg bodyweight) within 30 min.

Phase 3: Infusion of glucose 5% over 40-60 min. 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	

Model Structure

- Sodium drives copeptin release / production
- Glucose change from baseline influences sodium elimination



Model Equations

$$\frac{d}{dt}Glu(t) = Inf_{Glu}(t) - kel_{Glu} \cdot Glu(t) \qquad Glu(0) = GluBase$$

$$\frac{d}{dt}Sod(t) = Inf_{Glu}(t) - kel_{Sod} \cdot \left(1 + ch_{Glu}(t)\right) \cdot Sod(t) \qquad Sod(0) = SodBase$$

$$\frac{d}{dt}Cop(t) = Cop_{Rel}(t) - kel_{Cop} \cdot Cop(t) \qquad Cop(0) = CopBase$$

$$Cop_{Rel}(t) = \left(\frac{Sod(t)}{V_{Sod}} - SodBase\right) \cdot \begin{cases} k_{inA} & for\ phase = 1 \\ k_{inB} & for\ phase > 1 \end{cases}$$

$$ch_{Glu}(t) = \left(\frac{Glu(t)}{V_{Glu}} - GluBase\right)$$

Model was implemented in MONOLIX 4.3

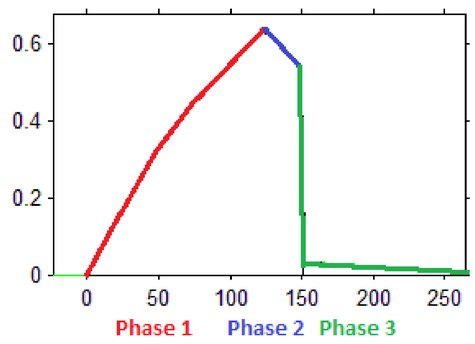
Results

Copeptin release gets stimulated during sodium infusion (phase 1), strongly decreases during waterload (phase 2) and immediately stops when glucose infusion starts (phase 3).

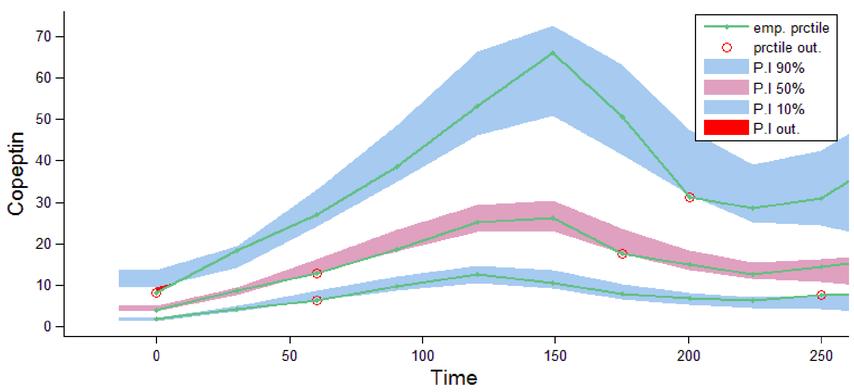
Covariates: Weight affects V_{Sod} and V_{Glu}. Gender influenced V_{Sod} and copeptin at baseline.

Parameter [unit]	Estimate (rse)	BSV (rse)
$V_{Sod}[L]$	74.4 (4)	0.16 (13)
$kel_{Sod}[min^{-1}]$	6.74E-3 (5)	0.35 (11)
$SodBase[mmol\ L^{-1}]$	140 (0)	0.01 (10)
$V_{Glu}[L]$	68.8 (4)	0.31 (11)
$kel_{Glu}[min^{-1}]$	1.34E-2 (11)	0.76 (12)
$GluBase\ [mmol\ L^{-1}]$	4.88 (1)	0.08 (8)
$kel_{Cop}[min^{-1}]$	1.83E-2 (6)	0.36 (9)
$CopBase\ [pmol\ L^{-1}]$	3.48 (10)	0.63 (8)
$k_{inA}\ [min^{-1}]$	5.67E-2 (7)	0.63 (8)
$k_{inB}\ [min^{-1}]$	3.13E-3 (51)	---
$\beta\_V_{Sod}\_Gender$	0.22 (27)	
$\beta\_V_{Sod}\_Weight$	0.61 (30)	
$\beta\_V_{Glu}\_Weight$	0.69 (35)	
$\beta\_CopBase\_Gender$	0.56 (25)	

Typical shape of copeptin release $CopRel(t)$:



VPC of copeptin:



Conclusions

- First semi-mechanistic model characterizing kinetics of the new biomarker copeptin and sodium related increase in central copeptin release in healthy subjects
- Such a model can be extended to characterize copeptin in paediatric and adult patients with diabetes insipidus