Quantification of tetracosactide (synthetic ACTH) pharmacokinetics and its effects on cortisol production in healthy adults and children.

Y. Mirasbekov[1,2], D. Bindellini[1,2], C. Elder[3], W. Huisinga[2,4], R. Michelet[1], C. Kloft[1,2]

(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany,
(2) Graduate Research Training program PharMetrX, Berlin/Potsdam, Germany,
(3) University of Sheffield, United Kingdom,
(4) Institute of Mathematics, University of Potsdam, Germany.

Background

ACTH-cortisol homeostasis [1]

- ACTH-stimulated cortisol production
- Follows a circadian rhythm
- Cortisol-mediated suppression of ACTH secretion

Congenital adrenal hyperplasia [1]

- Impaired cortisol synthesis
- Compensatory ACTH excess
- Often requires lifelong cortisol replacement therapy

Synthetic ACTH [2,3]

- Tetracosactide (Synacthen®)
- Analogue of endogenous ACTH.
- Used to test adrenal function (short Synacthen test)

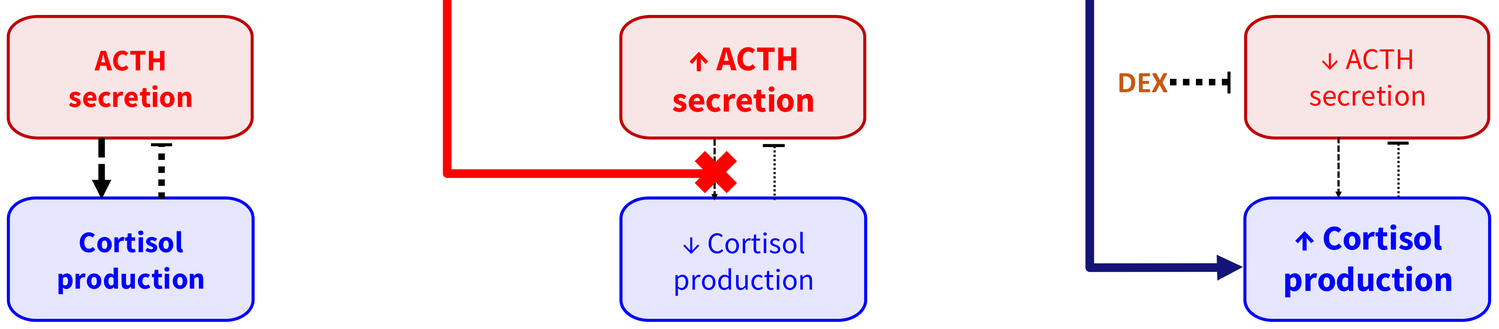

Fig. 1 ACTH-Cortisol Regulation: Homeostasis, CAH disruption, and synthetic ACTH stimulation in the study.

Objectives

To understand ACTH-driven endogenous cortisol production in adults and children

- Develop a tetracosactide pharmacokinetic model
- Integrate into a previously developed ACTH-cortisol dynamics model in adults
- Evaluate model applicability to the paediatric population

Methods

Study design [3]

- Healthy adults
- Male
- 19-46 years
- Tetracosactide doses:
  1 µg (LDT, n=23)
  250 µg (HDT, n=12)

- Healthy children
- Female & male
- 5-14 years
- Tetracosactide doses:
  1 µg (LDT, n=12)
  145 µg/m² (HDT, n=12)

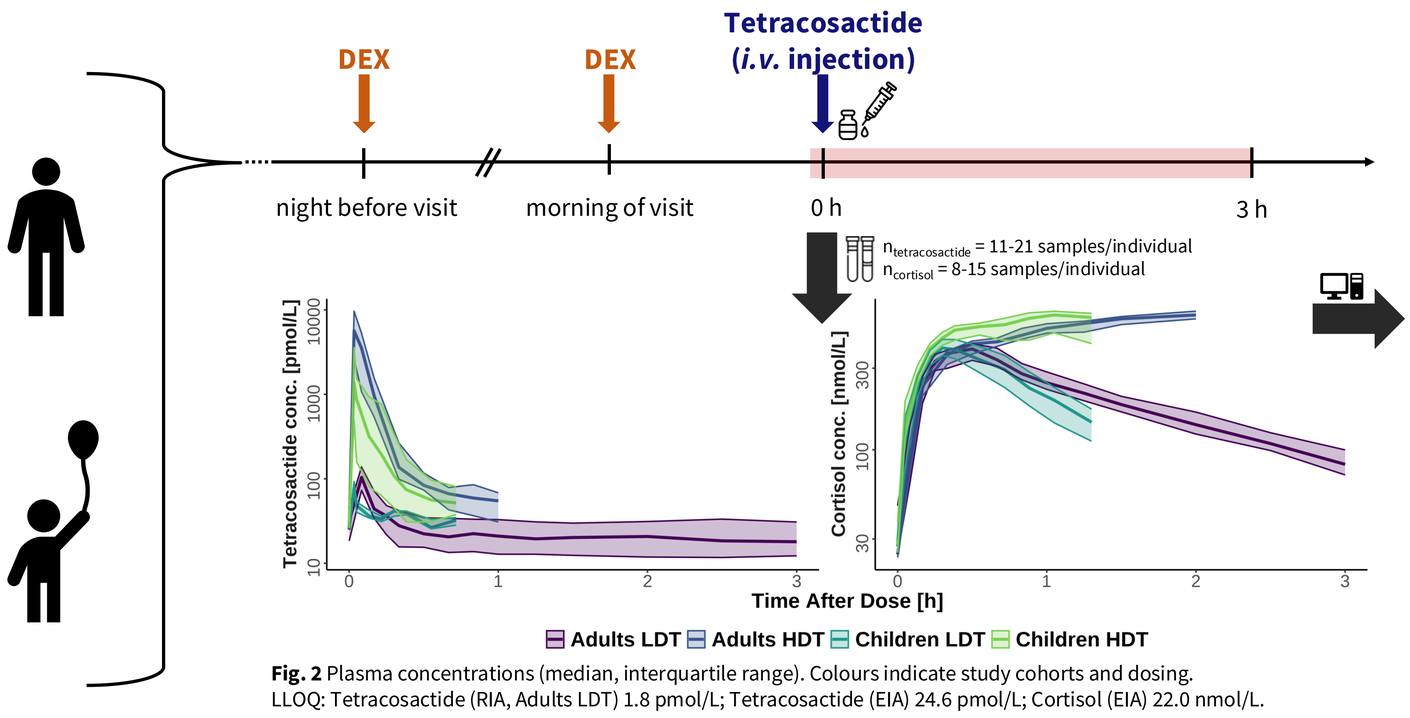

Fig. 2 Plasma concentrations (median, interquartile range). Colours indicate study cohorts and dosing.
LLOQ: Tetracosactide (RIA, Adults LDT) 1.8 pmol/L; Tetracosactide (EIA) 24.6 pmol/L; Cortisol (EIA) 22.0 nmol/L.

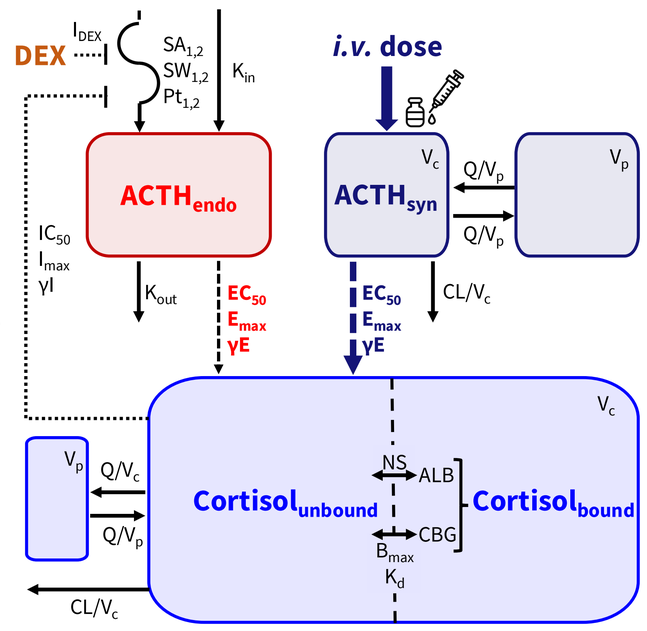

Fig. 3 Schematic overview of ACTH-cortisol dynamics model, including dexamethasone administration and PK model of tetracosactide. Adapted from Bindellini *et al.*, 2024 [5].

Results

Pharmacokinetics of tetracosactide

- Two-compartment model with linear elimination and theory-based allometric scaling (Fig. 4, Table 1)

Pharmacodynamics of cortisol production

- Original model acceptably predicted plasma cortisol in healthy adults (Fig. 5)

- Re-estimated model showed decreased maximum cortisol production rate constant (Fig. 6-7, Table 2)

Table 1. Parameter estimates of PK model of tetracosactide.

Parameter	Unit	Estimates	RSE [%] (SIR)
Baseline†	[pmol/L]	20.2	7.60
CL (70 kg)	[L/h]	28.0	12.0
V_c (70 kg)	[L]	0.474	12.7
Q (70 kg)	[L/h]	11.1	17.9
V_p (70 kg)	[L]	1.24	14.6
Interindividual variability parameters [CV, %]			
ω Baseline†		64.6	22.2
ω CL		77.5	17.6
Residual unexplained variability parameters [CV, %]			
σ Proportional		70.3	2.92

†Assay-specific signal

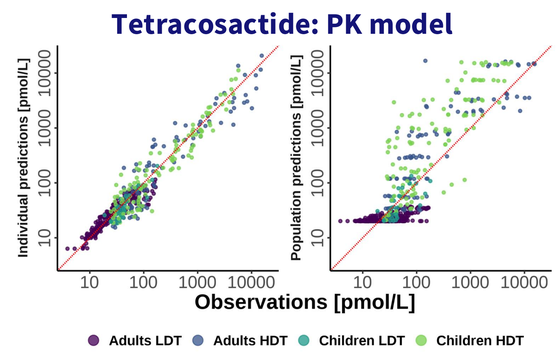

Fig. 4 GOF plot for PK model of tetracosactide. Colours indicate study cohorts and dosing.

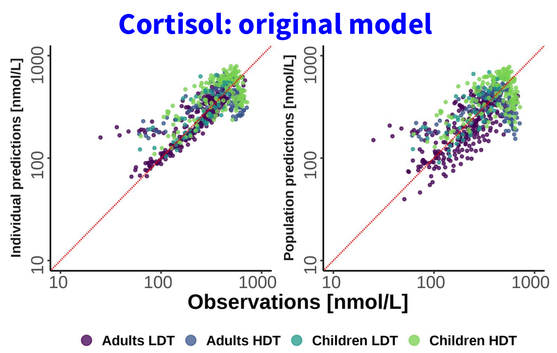

Fig. 5 GOF plot for PD model of cortisol production (E_{max} = 5400 nmol/h; OFV = -369).

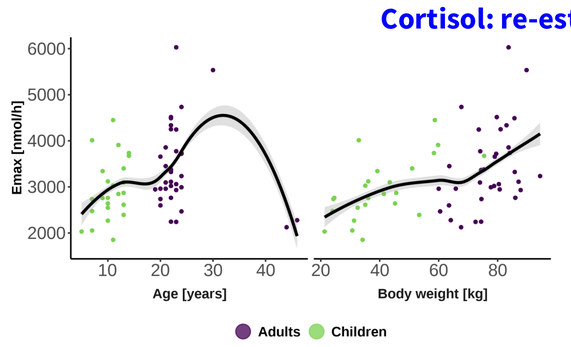

Fig. 6 Individual E_{max} vs. age and body weight. Colours indicate study cohorts. (E_{max} = 3105 nmol/h; 31.6% CV IIV; OFV = -634).

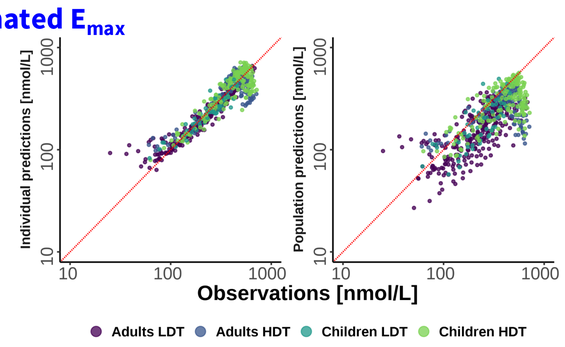

Fig. 7 GOF plot for re-estimated model ($E_{max,adults}$ = 3476 nmol/h; $E_{max,children}$ = 2988 nmol/h; 25.6% CV IIV; OFV = -645).

Table 2. Parameter estimates of PD model of cortisol production based on the ACTH-cortisol dynamics model [4,5].

Parameter	Unit	Estimates	RSE [%] (SIR)
	Cortisol Disposition		
Baseline Cortisol	[nmol]	21.9	16.2
CL (70 kg)	[L/h]	106*	-
V_c (70 kg)	[L]	2.15*	-
Q (70 kg)	[L/h]	89.9*	-
V_p (70 kg)	[L]	61.7*	-
NS_{ALB}	-	4.15*	-
$K_{d,CBG}$	[nmol/L]	9.71*	-
	Cortisol Production		
Baseline $ACTH_{endo}$	[pmol/L]	1.29*	-
$E_{max,\ adults}$	[nmol/h]	3476	4.69
$E_{max,\ children}$	[nmol/h]	2988	5.56
EC_{50}	[pmol/L]	6.63*	-
γE	hill factor	2.94*	-
Interindividual variability parameters [CV, %]			
ω Baseline Cortisol		155	28.9
ω CL		11.4*	-
ω V_c		12.2*	-
ω Baseline $ACTH_{endo}$		24.6*	-
ω E_{max}		25.6	31.5
ω EC_{50}		27.6*	-
Residual unexplained variability parameters [CV, %]			
σ Proportional		53.9	2.56

* Fixed parameters

Discussion and Conclusions

Using the previously developed **ACTH-cortisol dynamics model**, **PK/PD model of tetracosactide** described concentration-time profiles of plasma tetracosactide and cortisol**.**

Maximum cortisol production rate constant was lower in the paediatric population, which can potentially be explained by body weight descriptors. This work provides initial insights into the differences in **cortisol production between adults and children**.

References

[1] Merke and Auchus, N. Engl. J. Med. (2020)
[2] Alía *et al.*, Clin. Endocrinol. (2006)
[3] Elder *et al.*, JCEM (2020)
[4] Melin *et al.*, Clin. Pharmacokinet. (2018)
[5] Bindellini *et al.*, J. Pharmacokinet. Pharmacodyn. (2024)

Abbreviations

ACTH	Adrenocorticotropic hormone
ALB	Albumin
CBG	Corticosteroid binding globulin
CV	Coefficient of variation
CI	Confidence interval
CL/Q	Clearance/Intercompartmental clearance
DEX	Dexamethasone
EC_{50}	ACTH conc. at half-maximum cortisol production
EIA/RIA	Enzymatic immunoassay/Radioimmunoassay
E_{max}	Maximum cortisol production rate constant
γE	Hill factor for cortisol production
GOF	Goodness-of-fit
HDT	High-dose test
i.v.	Intravenous
K_d	Dissociation constant cortisol-CBG
LDT	Low-dose test
LLOQ	Lower limit of quantification
NS	Nonspecific binding cortisol-ALB
OFV	Objective function value
RSE	Relative standard error
SIR	Sampling importance resampling
$V_{c/p}$	Volume of distribution, central/peripheral

For more information:
Yersultan Mirasbekov,
yersultan.mirasbekov@fu-berlin.de
www.clinical-pharmacy.eu

Population Approach Group Europe 33rd PAGE meeting, Thessaloniki 2025