Comparison of immediate- and modified-release hydrocortisone to achieve therapeutic goals in congenital adrenal hyperplasia

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Background

Healthy

ACTH stimulates **cortisol** production following a circadian rhythm
Cortisol suppresses ACTH secretion to maintain hormonal homeostasis[1,2]

Disease

Congenital adrenal hyperplasia (**CAH**): Genetic rare disease
Impaired cortisol production and consequent **ACTH** (and sex hormones) **excess secretion**[1,2]
Severe cases require **therapy from birth**

Therapy

Replacement therapy: **Hydrocortisone** (**HC**, synthetic cortisol)
Immediate-release **(IR) HC**: Fails to mimic cortisol circadian rhythm often resulting in poor disease management
15-25 mg/day divided in 2-3 doses[1,3]
Modified-release **(MR) HC**: Developed to improve mimicking early morning increase in cortisol concentrations
15-25 mg/day twice daily (2/3 before sleep, 1/3 at waking)[1]

Goals

Mimicking physiological cortisol concentrations
Reducing ACTH excess secretion
Quantitative understanding of disease-therapy interaction is lacking, limiting therapy optimisation

Objectives

Characterise MR HC absorption kinetics: Integrate into previously developed ACTH-cortisol dynamics and IR HC pharmacokinetic model[4]

Comprehensive **evaluation** and comparison of **IR and MR HC dosing regimens** based on **therapeutic goals achievement**

Methods

Clinical trial data

N=18 + DEX + MR HC
- 20 mg (8 am)

N=16 + DEX + MR HC
- 5 mg (11 pm)
- 10 mg (11 pm)
- 20 mg (11 pm)
- 20 mg (11 pm) + 10 mg (7 am)

MR HC absorption modelling

- **BASE MODEL**: Based on morning single-dose data: Investigate gastric emptying functions and transit compartments number
- **NIGHT SINGLE-DOSE DATA**: Separate parameter set for night single-dose data
- Evaluate sharing parameters (morning and night kinetics)
- **TWICE-DOSING DATA**: Re-estimation of all MR HC absorption parameters

Simulations of ACTH-cortisol

Healthy individual: **100% cortisol production**
+ IR HC: **First dose:** 5 am, 6 am or 7 am; **Dosing interval:** 4, 5 or 6 hours; **Daily dose:** 15, 20 or 25 mg/day (2:1:1 ratio)
27 IR HC dosing regimens

CAH Patient: **0% cortisol production**
+ MR HC: **Evening (first) dose:** 15, 20 or 25 mg at 10 pm, 11 pm or 12 pm; **Morning dose:** 5, 10 or 15 mg at 6 am, 7am or 8 am
48 MR HC dosing regimens

Evaluation of therapeutic goals achievement

Similarity to healthy cortisol profiles

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}\left(x_i - x_{i,healthy}\right)^2}{n}}$$

$$Similarity\% = \frac{RMSE - RMSE_{untreated}}{RMSE_{healthy} - RMSE_{untreated}} \cdot 100$$

ACTH AUC reduction compared to untreated CAH patient

$$AUC\ reduction\% = \frac{AUC_{untreated} - AUC}{AUC_{untreated}} \cdot 100$$

Results

MR HC absorption described by **sigmoidal gastric emptying onset model** followed by **4 transit compartments** (Fig. 1, "MR HC")

Absorption kinetics differences identified between **morning and night doses** (Fig. 2, Table 1)

MR HC showed **higher similarity to healthy cortisol** and far **higher ACTH AUC suppression** compared to IR (Fig. 3)
ACTH AUC **suppression by IR dependent on time** of first dose (Fig. 3)

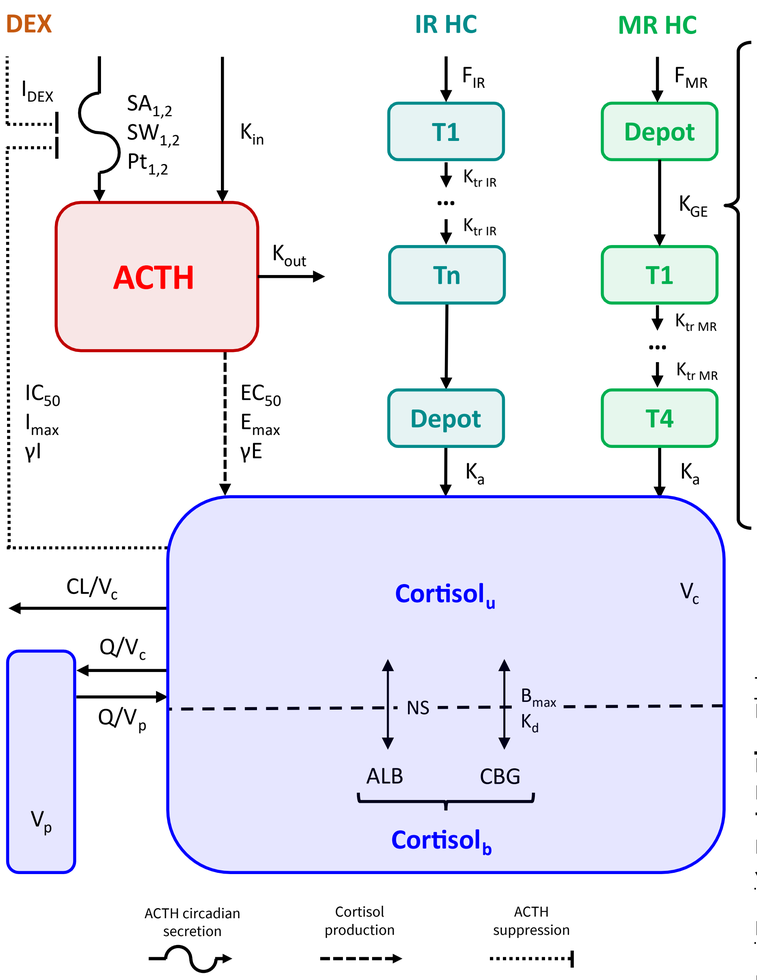

Fig. 1 Schematic overview of the integrated modelling framework (ACTH-cortisol dynamics, IR and MR HC pharmacokinetics)

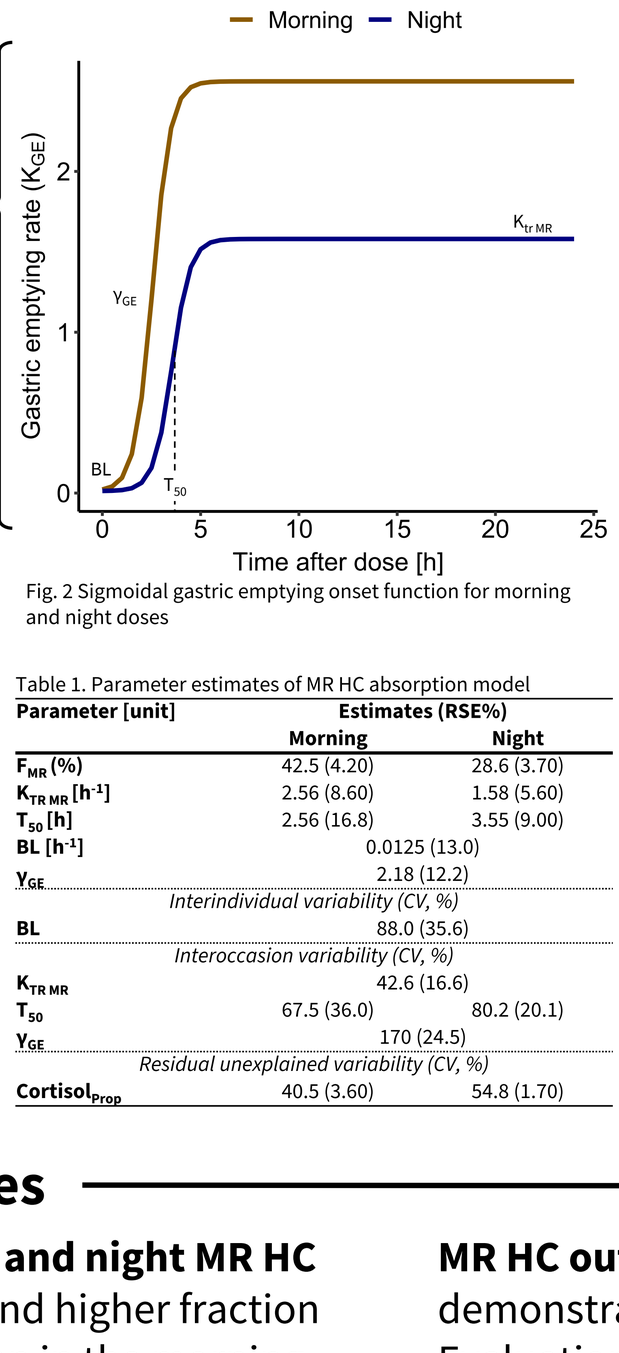

Fig. 2 Sigmoidal gastric emptying onset function for morning and night doses

Table 1. Parameter estimates of MR HC absorption model

Parameter [unit]	Estimates (RSE%)	
	Morning	Night
F_{MR} (%)	42.5 (4.20)	28.6 (3.70)
$K_{TR\ MR}$ [h^{-1}]	2.56 (8.60)	1.58 (5.60)
T_{50} [h]	2.56 (16.8)	3.55 (9.00)
BL [h^{-1}]	0.0125 (13.0)	
$γ_{GE}$	2.18 (12.2)	
Interindividual variability (CV, %)		
BL	88.0 (35.6)	
Interoccasion variability (CV, %)		
$K_{TR\ MR}$	42.6 (16.6)	
T_{50}	67.5 (36.0)	80.2 (20.1)
$γ_{GE}$	170 (24.5)	
Residual unexplained variability (CV, %)		
$Cortisol_{Prop}$	40.5 (3.60)	54.8 (1.70)

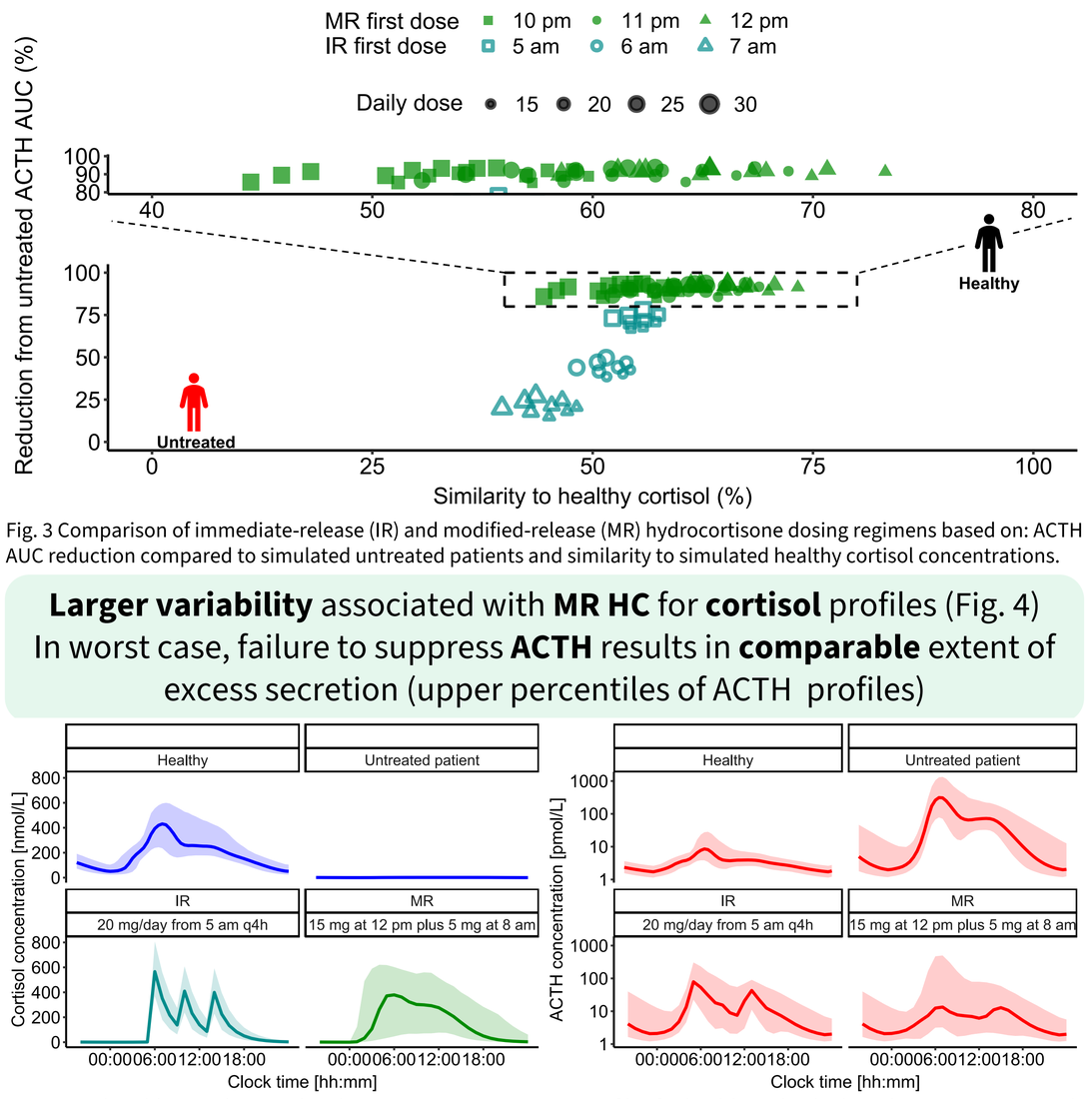

Fig. 3 Comparison of immediate-release (IR) and modified-release (MR) hydrocortisone dosing regimens based on: ACTH AUC reduction compared to simulated untreated patients and similarity to simulated healthy cortisol concentrations.

Larger variability associated with **MR HC** for **cortisol** profiles (Fig. 4)
In worst case, failure to suppress **ACTH** results in **comparable** extent of excess secretion (upper percentiles of ACTH profiles)

Fig. 4 Simulated (n=1000) cortisol and ACTH concentration-time profiles for healthy individuals and patients: Untreated, following IR HC administration and following MR HC administration. Solid line: Median of the simulated profiles. Shaded area: 5th-95th percentiles of the simulated profiles.

Discussion and Perspectives

Identified **differences** between **morning and night MR HC absorption kinetics**: Faster absorption and higher fraction available for absorption when MR HC given in the morning

MR HC outperformed IR HC at achieving both therapeutic goals demonstrating **higher potential for improved therapeutic outcome**: Evaluation of similarity to healthy cortisol only would be misleading

[1] van der Grinten *et al.* Endocr. Rev. (2022)
[2] Merke *et al.* N. Engl. J. Med. (2020)
[3] Speiser *et al.* J. Clin. Endocrinol. Metab. (2018)
[4] Bindellini et al. J. Pharmacokinet. Pharmacodyn. (2024)

Abbreviations: ALB: Albumin, BL: Baseline gastric emptying rate, CBG: Corticosteroid binding globulin, $Cortisol_b$: Bound cortisol, $Cortisol_u$: Unbound cortisol, DEX: Dexamethasone, K_{GE}: Sigmoidal gastric emptying onset function, $γ_{GE}$: Hill factor gastric emptying onset, I_{DEX}: Dexamethasone-driven ACTH suppression, $K_{tr\ MR}$: Maximal gastric emptying rate constant, NS: Nonspecific binding cortisol-albumin, Pt: Peak time surge, SA: Amplitude surge, SW: Width surge, T_{50}: Time to reach 50% of $K_{tr\ MR}$.

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