

Rationale for a reduced dexamethasone dose in prenatal congenital adrenal hyperplasia therapy based on pharmacokinetic modelling

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INTRODUCTION

Prenatal dexamethasone (Dex) therapy is used in female fetuses with congenital adrenal hyperplasia (CAH) to suppress adrenal androgen excess and prevent virilisation of the external genitalia. Despite the risks for the treated mother and potentially for the unborn child, no clinical study or evaluation had been conducted in order to determine a Dex dose with a scientific rationale.

AIM

To investigate a rationale of a reduced Dex dose in prenatal CAH therapy based on a pharmacokinetics-based modelling and simulation framework.

METHOD

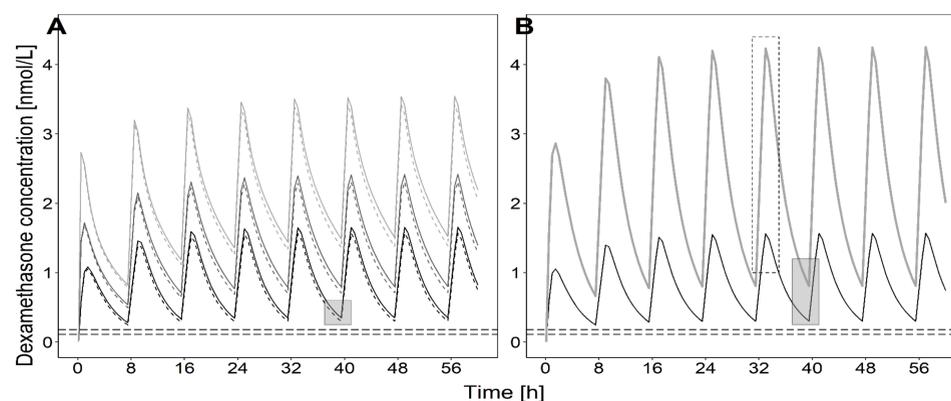
Using data from a published Dex study a nonlinear mixed-effects model describing maternal dexamethasone pharmacokinetics (PK) was developed.

In stochastic simulations (n=1000), a typical pregnant population (n=124) was split into two dosing arms receiving the

- traditional 20 µg/kg/d Dex dose or
 - reduced doses between 5 and 10 µg/kg/d.
- Target maternal Dex concentrations, ensuring foetal hypothalamic-pituitary-adrenal axis suppression, were identified from literature and served as threshold to be exceeded by 90% of mothers at steady state.

RESULTS

A two-compartment dexamethasone pharmacokinetic model was successfully developed and evaluated. The simulations, as well as a sensitivity analysis regarding the assumed foetal:maternal dexamethasone concentration ratio, resulted in 7.5 µg/kg/d to be the minimum effective dose and thus our recommended dose.



Dexamethasone (Dex) concentration–time profiles after administration of (A) 7.5 µg/kg/day as reduced dose for light (50–72 kg, dashed lines) and heavy (73–95 kg, solid lines) body weight groups (n = 62 patients per group with n = 1000 simulations each) with 10th percentile (black lines), median (dark grey lines) and 90th percentile (light grey lines), (B) 7.5 µg/kg/day as reduced dose (black solid line of A) and traditional dose (20 µg/kg/day, grey line) of 10 percentiles and light body weight group only. Dashed horizontal lines: Dex threshold concentration if Dex is 50- (upper line) or 80-fold (lower line) more potent than cortisol, light grey filled boxes: minimum Dex concentration at steady state, dashed non-filled box: maximum Dex concentration at steady state. Arrows: Dex dose administrations before (dashed arrows) and after (solid line arrows) steady state.

CONCLUSIONS

Based on our modelling and simulation results, the current experimentally used Dex dose seems 3-fold higher than needed, resulting in unnecessary high risks for treated mothers and fetuses. The clinical relevance and appropriateness of this reduced Dex dose during pregnancy will be tested in a prospective international clinical trial.

OUTLOOK

PREDICT – PREnatal Dexamethasone In Congenital adrenal hyperplasia Therapy is a European multicenter study under the direction of Prof. Dr. Nicole Reisch, Munich, funded by the German Federal Ministry of Education and Research to investigate the effect and safety of a reduced Dex-dose in prenatal congenital adrenal hyperplasia. There will be two intervention groups (Dex dose 20 µg/kg/d versus 7.5 µg/kg/d starting at gestational week 5-7 post conceptionem compared to a non-intervention group.

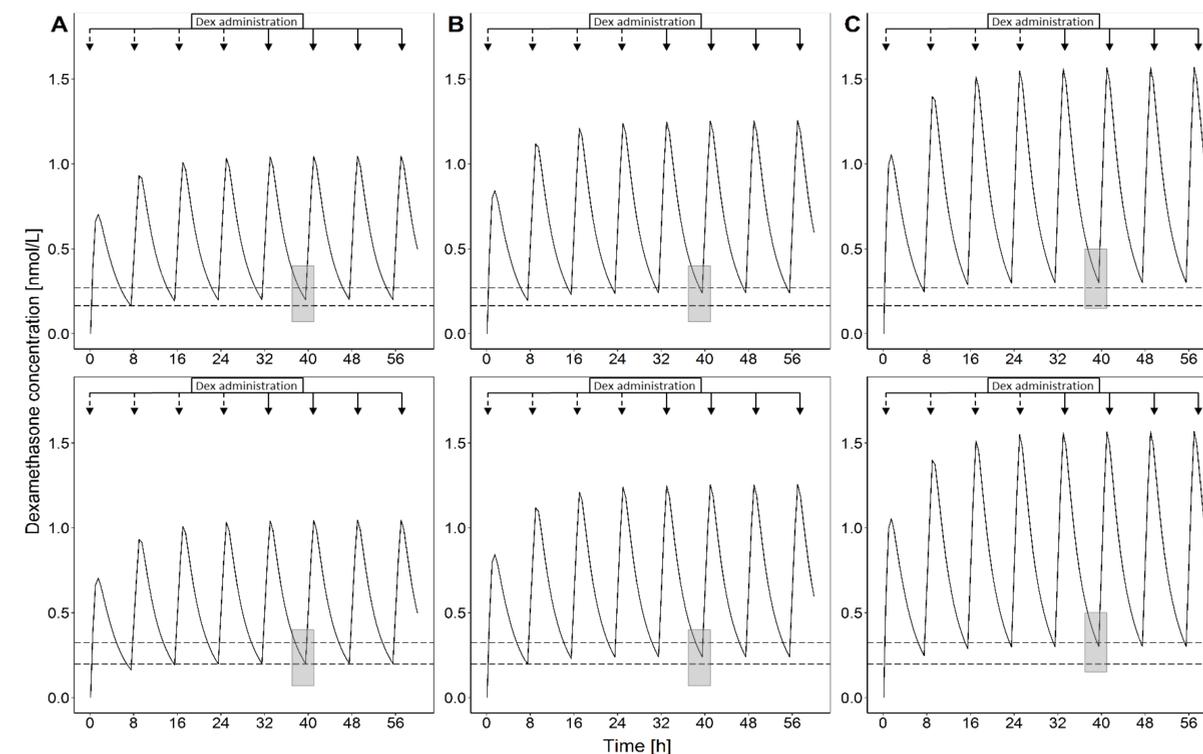
Planned starting date: in the spring of 2022

REFERENCES

Stachanow V et al., Rationale of a lower dexamethasone dose in prenatal congenital adrenal hyperplasia therapy based on pharmacokinetic modelling. Eur J Endocrinol. 2021;185(3):365-374.

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Sensitivity analysis for foetal:maternal Dex concentration ratio. Simulated 10th percentile Dex concentration–time profiles of light (50–72 kg) body weight group (n = 62 patients) after administration of reduced doses with 5 (A), 6 (B) and 7.5 (C) µg/kg/day, if foetal:maternal Dex concentration ratio = 0.3 (top) or 0.25 (bottom) instead of 0.45 (ratio retrieved from literature). Dashed horizontal lines: Dex threshold concentration if Dex is 50- (upper line) or 80-fold (lower line) more potent than cortisol, light grey boxes: minimum Dex concentration at steady state. Arrows: Dex dose administrations before (dashed arrows) and after (solid line arrows) steady state.