

Atypical prednisone-metabolism: Pharmacological studies in a boy with classical adrenal hyperplasia and suspected malcompliance

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Background

We present the long-term clinical course of a boy with classical adrenal hyperplasia (CAH) with constantly increased 17-OH-progesterone (17-OH-P) in puberty despite multiple dose adjustments of hydrocortisone (HC).

Pharmacokinetic studies lead to a new therapy regimen with significant improvement of his markedly raised androgen levels.

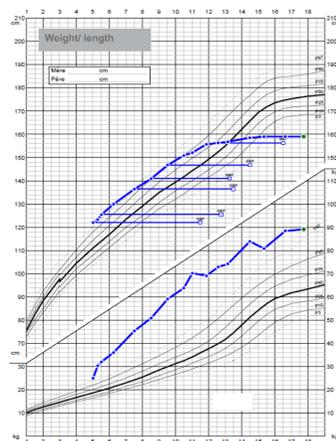
Patient

First **clinical presentation** at the age of 5 years:

- Peripheral precocious puberty
- Accelerated growth rate (>P97)
- Bone age: 12 6/12 years

Laboratory evaluation at first clinical presentation:

- 17-OH-progesterone: >350nmol/l (N<6);
- DHEA-S 7.1umol/l (N<3)
- androstendione 25nmol/l (N 0.3-1.7)
- electrolytes: normal values



Diagnosis of CAH was made

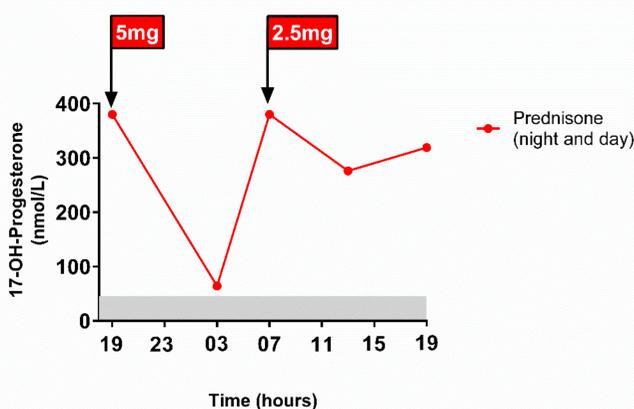
CHILDHOOD: Well-controlled under HC 15-18mg/m² body surface
PUBERTY: *Problems started!* Insufficient control of androgens, therefore changing from HC to prednisone. But: problems remained! Non-compliance was suspected as cause of the inadequately controlled CAH. OR: an atypical steroid metabolism was considered.

Method

To distinguish between non-compliance with insufficient intake of prednisone and an atypical metabolism of prednisone/ prednisolone a 24hour pharmacokinetic study of prednisone and prednisolone metabolism was performed.

Result I

STEP 1 ANALYSIS OF 24-HOUR 17-OH-P KINETICS
Prednisone 7.5mg/d



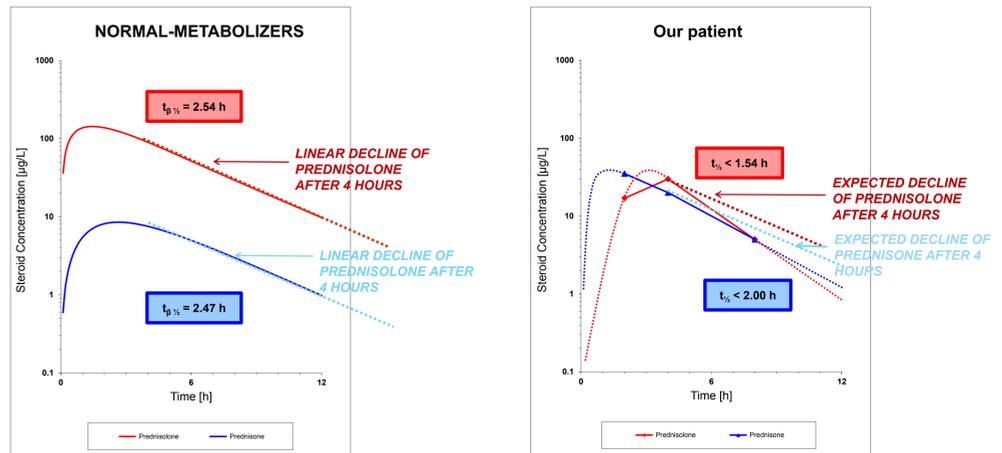
Conclusion I:

- Prednisone leads to a suppression of 17-OH-P in the first 8 hours after intake
- However, an early rise of 17-OH-P is observed, resulting in elevated 17-OH-P about 12 hours later
- So, the «usual» 12-hour dosing intervals of prednisone are insufficient in our patient.
- But why?**

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Results II

STEP 2 ANALYSIS OF PREDNISONE/ PREDNISOLONE METABOLISM IN «NORMAL-METABOLIZERS» AND OUR PATIENT

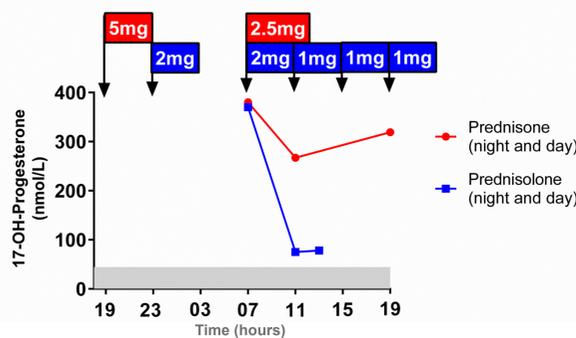


Conclusion II: Our patient is:

- a slow «hydroxylater» of prednisone to prednisolone, leading to the later and weaker prednisolone peak together with a higher prednisone peak in the first 1-2 hours compared to «normal-metabolizers», AND;
- a fast metaboliser of prednisolone, as shown in the sharper decline of prednisolone- and prednisone levels in our patient after 4 hours.

Results III

STEP 3 IMPROVING DAYTIME 17-OH-P
Prednisolone every 4 h instead of Prednisone every 12 h

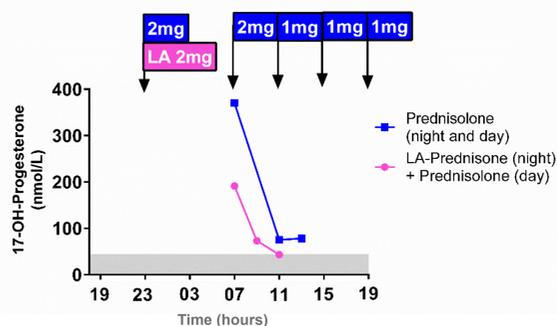


Conclusion III:

- Changing from prednisone to prednisolone together with shorter dosing-intervals already lead to a significant improvement of 17-OH-P during daytime
- But: morning is still a problem!**

Results IV

STEP 4 IMPROVING NIGHTTIME AND MORNING 17-OH-P
Long-acting Prednisone instead of Prednisolone at bedtime



Conclusion IV:

- Now: Solving the morning problem: Introduction of long-acting prednisolone in the evening, resulting in significant improved 17-OH-P in the morning!
- To be perfect: pump therapy! But refused by patient.**

Conclusion

- Before blaming a patient with CAH on non-compliance due to raised 17-OH-P values, a pharmacokinetic study might be helpful to detect patients with atypical steroid metabolism.
- Modulated release prednisone formulation is a helpful tool to cover the longer period at night time and avoid raise of 17-OHP and ACTH in the early morning.

