Quantitative urinary GC-MS based steroid analysis for treatment monitoring of adolescents and young adults with autoimmune primary adrenal insufficiency

Clemens Kamrath, Michaela F. Hartmann and Stefan A. Wudy

Justus-Liebig-University, Centre of Child and Adolescent Medicine, Division of Pediatric Endocrinology and Diabetology, Steroid Research & Mass Spectrometry Unit, Giessen, Germany

Background

Primary adrenal insufficiency (PAI) is a rare and life-threatening disease. About 50% of adolescents and young adults (AYAs) with chronic diseases are non-adherent to their prescribed treatment regimens [1,2]. Therefore, suitable hormonal monitoring of glucocorticoid replacement would be desirable in AYAs with PAI.

Objective and hypotheses

Quantitative targeted GC-MS urinary steroid metabolome analysis for treatment monitoring for AYAs with autoimmune PAI [3].

Methods

We retrospectively analyzed 21 24-hr urinary steroid metabolome analysis of four AYAs aged 15.6 ± 2.0 years with autoimmune PAI on hydrocortisone and fludrocortisone treatment. 24-hr urinary cortisol metabolite excretion rates (CMER) were calculated and transformed into z-scores (**Fig. 1**).

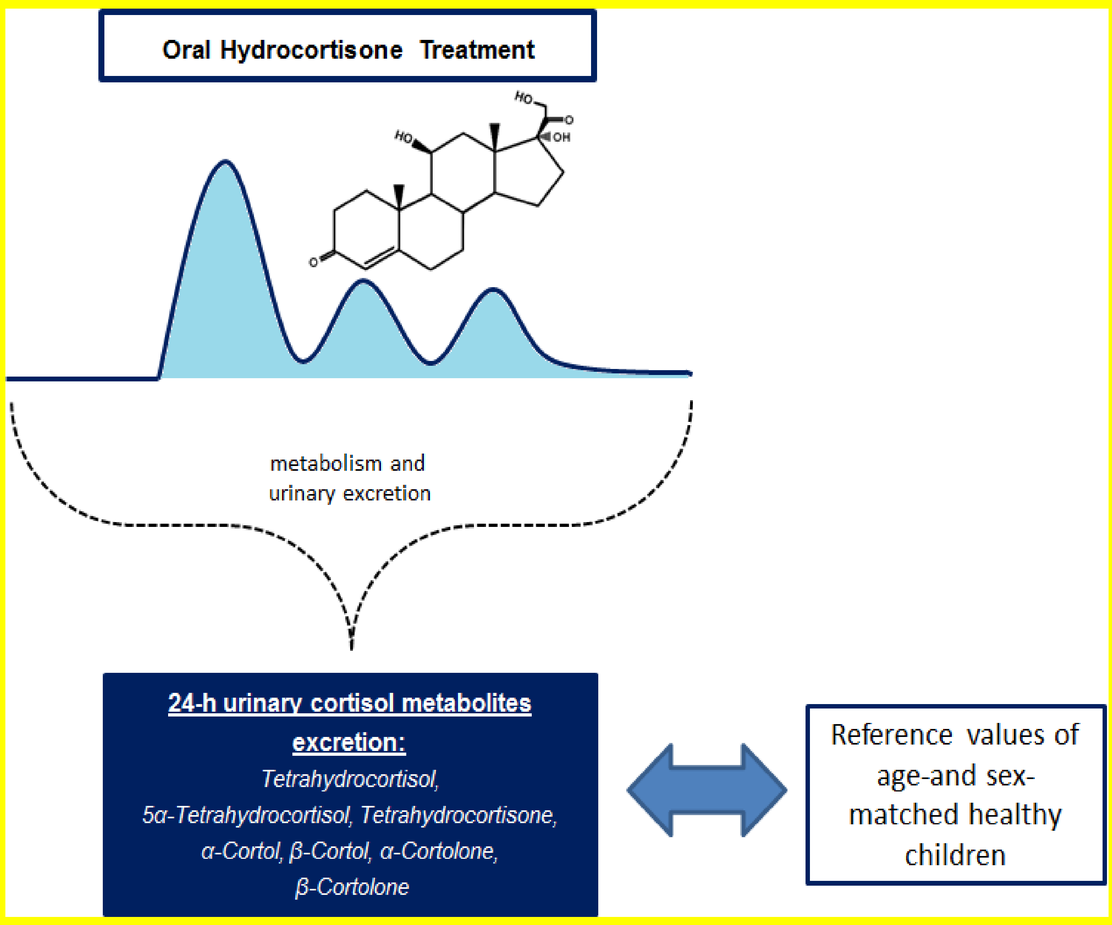
Results

Three patients (#1-3) showed good treatment adherence (17 of 21 samples). Mean CMER of these samples was 7.4 ± 1.8 mg/ m^2/d, corresponding to a z-score of 1.8 ± 1.1 (**Fig. 2B**). CMER reflected 59.7 ± 14.5% of prescribed hydrocortisone dosages (**Fig. 2A**).

The forth patient (#4, female) initially showed an adequate treatment-adherence with a CMER of 5.2 mg/ m^2 BSA/d, consistent with z-scores of 0.8 and 0.6 for absolute and BSA-corrected values, respectively (**Fig 2B**; green circle). CMER reflected 49.4% of the prescribed hydrocortisone dosage (**Fig 2A**; green circle).

The patient later displayed clinical symptoms of PAI during treatment (marked by an arrow). Her CMER was only 0.3 mg/ m^2 (-3.4 z), reflecting only 3.1% of prescribed hydrocortisone dosage. She admitted that she had interrupted treatment. Later controls showed somewhat better but still inadequate adherence. CMERs were 3.6 mg/ m^2/d (-0.3 z; 27.4 %) and 1.9 mg/ m^2/d (-1.6 z; 17.2%), respectively.

Figure 1

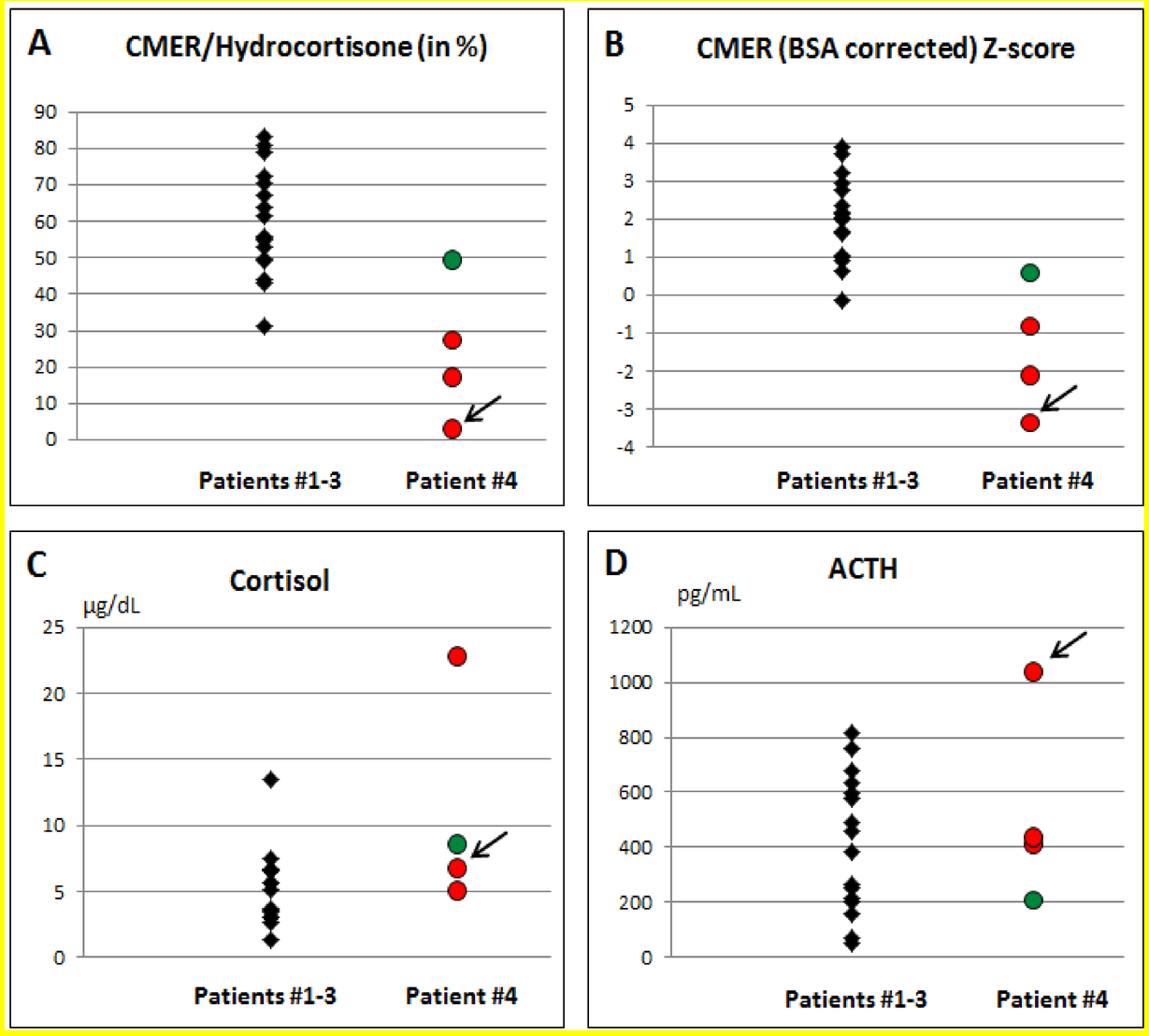


Hydrocortisone replacement treatment leads to timely dependent variable plasma cortisol concentrations. Therefore, periodic measurement of plasma concentrations of cortisol and ACTH is of limited value in patients with PAI. In contrast to the determination of single plasma samples, 24-hr quantitative targeted GCMS urinary steroid metabolome analysis of the sum of the major cortisol metabolites reflects integrated output of the daily hydrocortisone exposure. The results of 24-hr cortisol metabolite excretions were compared with reference values of age- and sex-matched healthy children [4] to determine adequate replacement dosage as well as, when compared with the prescribed hydrocortisone dosage, treatment adherence.

Conclusions

We could demonstrate that quantitative targeted GCMS steroid metabolome analysis is excellent suited to monitor glucocorticoid replacement treatment in patients with PAI. It allows assessment of treatment adherence and it helps to avoid over- and under treatment.

Figure 2



Values of patients #1-3 with known good treatment adherence were summarized at the left (black squares). The values of patient #4 were shown on the right (circles). At the first visit, treatment adherence was unremarkable (shown in green), thereafter, adherence was inadequate (red circles). Marked by an arrow: symptoms and signs of adrenal insufficiency were obvious and treatment was interrupted by the patients.

A. The relative amount (in percent) of urinary excreted cortisol metabolites in a 24-hr sample in relation to the prescribed daily oral hydrocortisone dosage served as a marker of treatment adherence. All samples of patients with adequate treatment adherence had values > 30%, whereas in all three samples of patient #4 with known inadequate adherence values were < 30%. Note that value was lowest in the sample taken from patient #4 after she had interrupted replacement treatment and complained about symptoms of PAI (indicated by an arrow).

B. Z-scores of 24-h CMER (BSA corrected). All samples of patients with adequate treatment adherence had values > -0.5 Z, whereas in all three samples of patient #4 with known inadequate adherence values were < -0.5 Z. Note that value was lowest in the sample taken from patient #4 while she complained about symptoms of PAI after she had interrupted (indicated by an arrow).

C. Plasma cortisol values. There was no difference between samples of patients with adequate or inadequate treatment adherence (reference value for morning samples: 5-20 µg/dL).

D. Plasma ACTH values. There was no difference between samples of patients with adequate or inadequate treatment adherence (reference value for morning sample: <46 pg/mL). Note that ACTH level was highest in the sample taken from patient #4 while she complained about symptoms of PAI after she had interrupted replacement treatment (indicated by an arrow).

References:

1. Kyngäs HA, Kroll T, Duffy ME. Compliance in adolescents with chronic diseases: a review. J *Adolesc Health*. 2000;26(6):379–388.
2. Meghan E. McGrady and Kevin A. Hommel. Medication Adherence and Health Care Utilization in Pediatric Chronic Illness: A Systematic Review. *Pediatrics.* 2013;132:730-40.
3. Wudy SA, Schuler G, Sanchez-Guijo A, Hartmann MF. The art of measuring steroids: Principles and practice of current hormonal steroid analysis. *J Steroid Biochem Mol Biol.* 2018;179:88-103.
4. Wudy SA, Hartmann MF, Remer T. Sexual dimorphism in cortisol secretion starts after age 10 in healthy children: urinary cortisol metabolite excretion rates during growth. *Am J Physiol Endocrinol Metab*. 2007;293:E970-6.

Disclosure: The authors have nothing to disclose