Endocrine (2019) 63:398–400
https://doi.org/10.1007/s12020-018-1780-4

LETTER TO THE EDITOR

Continuous subcutaneous hydrocortisone infusion in a woman with secondary adrenal insufficiency

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Keywords ACTH deficiency · Adrenal insufficiency · Cortisol · Circadian rhythm · Hydrocortisone · Subcutaneous infusion

Received: 18 June 2018 / Accepted: 1 October 2018 / Published online: 23 October 2018

Adrenal insufficiency requires long-term, often life-long, administration of 15–25 mg/day hydrocortisone in two to three daily doses, though personalized adjustments may be needed [1]. Disruption of the circadian cortisol rhythm is associated with poor quality of life, sleep disturbances, asthenia, immune disturbances, and impairment of glucose/lipid metabolisms. Programmable pumps may be used for continuous subcutaneous hydrocortisone infusion (CSHI) with modulated rates that mimic the circadian rhythm of serum cortisol concentrations [2]. We report the use of CSHI in a woman with secondary adrenal insufficiency (SAI) and multiple allergic reactions, including to excipients of the standard oral hydrocortisone tablet.

A 42-year-old woman (body weight: 64 kg, BMI: 22.2 kg/m^2, body surface area (BSA): 1.75 m^2), with secondary hypothyroidism and SAI from idiopathic ACTH deficiency (basal serum cortisol: 42 nmol/L, plasmatic ACTH: 1.83 pmol/L), was admitted to our Endocrine Unit because of profound asthenia, inability to cope with daily activities, hypotension, and nausea and vomiting in the morning. She was suffering from allergic reactions to several drugs, perfumes, cosmetics, solvents, and paints with previous episodes of anaphylaxis.

The oral administration of a 10-mg hydrocortisone tablet had previously induced an anaphylactic reaction with severe hypotension and laryngeal angio-oedema, which required hospitalization and adrenalin treatment. At the time of admission, substitutive therapy was 25 mg/day of a hydrocortisone preparation containing biologic rice amid, in four daily administrations.

Our CSHI protocol was approved by the local ethics committee (CEAS Regione Umbria, 3049/17). The Italian Health Ministry approved the use of a Medtronic MiniMed™ 640G (Medtronic MiniMed, 18000 Devonshire Street, Northridge, CA, USA) insulin infusion pump for CSHI in our patient (DGFDM.VI/P/I.5.i.n/2017/367). Written informed consent was obtained.

We chose a hydrocortisone preparation containing only sodium phosphate as excipient (Flebocortid® 500 mg/5 mL). The ampoule and the infusion kit were changed every 3 days. We initially set the infusion program according to available data in the literature (2), with a total daily hydrocortisone dose slightly lower than that used with the oral preparation. 7.00-am serum cortisol concentration ranged from 295 to 345 nmol/L in the first 3 days after CSHI was started and 24-h free urine cortisol was within the normal range (712 nmol/24 h). Subsequently, within the first 2 weeks, we gradually reduced the total daily dose of hydrocortisone (from the initial dose of 21.625 mg/day, 12.4 mg/m^2 BSA to 18.7 mg/day, 10.7 mg/m^2 BSA) and programmed a more gradual increase of cortisol infusion between 2.00 and 7.00 am, because of referred sleep disturbances.

During the following months, the patient experienced improvement of well-being with CSHI, with resolution of nausea and vomiting at wakening. She was also able to restart many of her home work and daily physical activities (including sport activities) that had been stopped after diagnosis of SAI. During 14 months of follow-up, she did not refer adverse reactions nor addisonian crisis, and all blood and urine values remained unchanged and within the normal range (including blood glucose, electrolytes, kidney/liver parameters, total cholesterol, high-density lypoproteins (HDL), low-density lypoproteins (LDL), and triglycerides). An adrenal insufficiency-specific quality-of-life questionnaire (AddiQoL-30) (score from 30 to 120) [3] scored 57 at baseline, 73 at 6-months, and 78 at 12-months CSHI.

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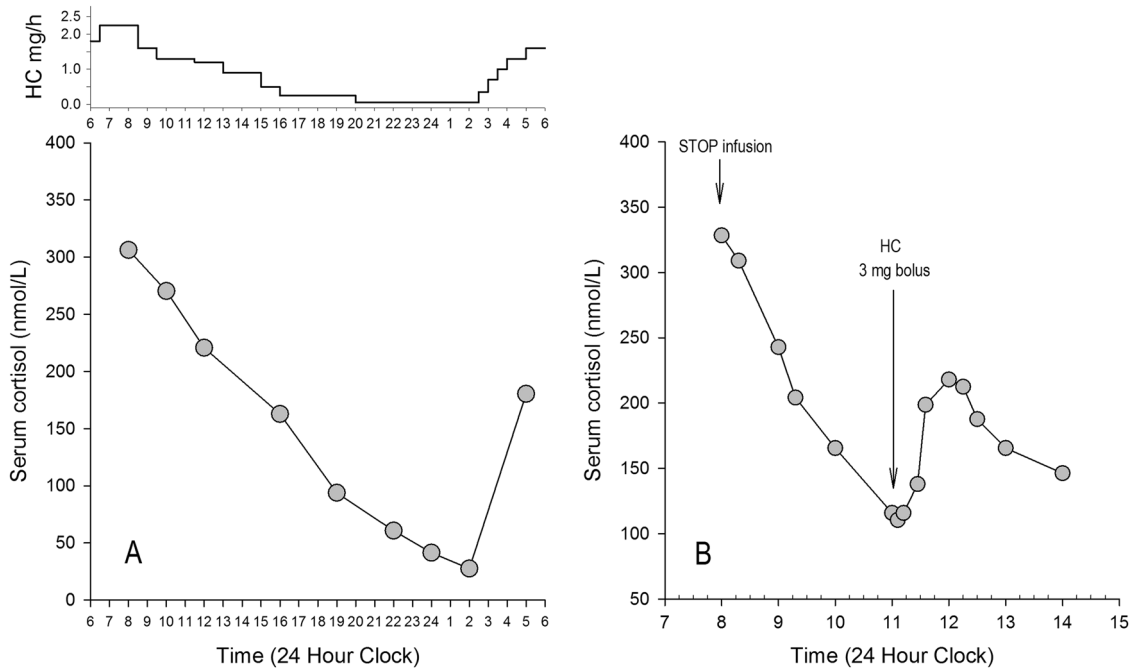

Fig. 1 **a** Infusion rates of hydrocortisone during continuous subcutaneous hydrocortisone infusion (CSHI) (upper panel) and serum cortisol profile during CSHI (lower panel). **b** Serum cortisol profile after stopping continuous subcutaneous hydrocortisone infusion (CSHI) at 8.00 am and after administration of a 3-mg hydrocortisone subcutaneous bolus

The AddiQoL subscale fatigue/energy level (AddiQoL-8) (score from 8 to 32) scored 9 at baseline, 15 at 6 months, and 18 at 12 months. We observed a slight increase in body weight (2 kg after 6 months and 3 kg after 12 months) as compared to baseline.

During the 14 months of continuous treatment, CSHI dose ranged from 18.5 to 18.9 mg/day (10.6–10.8 mg/m^2 BSA). Figure 1a shows the infusion protocol and cortisol serum concentrations after 6 months of CSHI (hydrocortisone dose 18.85 mg/day, 10.8 mg/m^2 BSA). CSHI infusion rate adjustments were based mainly on the patient's clinical response and well-being. We used cortisol profile only to confirm a correct circadian rhythm.

In pharmacokinetic studies (Fig. 1b), at 6 months, after stopping infusion at 8.00 am (serum cortisol: 328 nmol/L), we observed a 50% reduction of serum cortisol concentration after 120′ (165 nmol/L) and a 65% reduction after 180′ (116 nmol/L). After subcutaneous 3-mg bolus of hydrocortisone, serum cortisol concentration increased to 143 nmol/L at 30′ and to 199 nmol/l at 45′ with peak at 60′ (218 nmol/L). Serum cortisol concentration started to decline at 75′, with concentrations of 166 nmol/L after 2 h and 146 nmol/L after 3 h. These results provided important information for the patient to predict what could happen in the case of discontinuation of cortisol infusion during the morning. We instructed the patient to administer intramuscular 100 mg of the same hydrocortisone preparation used in CSHI in the case of severe hypotension [1] and to double all the infusion rates in the case of fever or other intercurrent illnesses.

Programmable pumps are non-CE-marked devices for CSHI. Specific approvals from the local ethics committee and the Italian Health Ministry were needed to perform CSHI in our patient on humanitarian grounds. Use of CSHI enables both a normalization of the serum cortisol profile and a dramatic reduction of total daily hydrocortisone dose with subsequent significant improvement of perceived quality of life (documented in our patient by the increase in AddiQoL score). Hence, CSHI can restore an almost-normal cortisol supplementation and may be instrumental in addressing specific and difficult clinical cases.

Compliance with ethical standards

Conflict of interest AF declares that he has received a speaker honorarium from Shire Italy S.p.A. The remaining authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient included in the study.

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