Consensus

Group 5: Acute adrenal insufficiency in adults and pediatric patients

Groupe 5 : insuffisance surrenale aigue chez le patient adulte et enfant

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1. Introduction

Acute adrenal insufficiency results from a relative or absolute deficiency in cortisol, secondary to an imbalance between increased requirement for hydrocortisone and an insufficient increase in its input. It is defined by an acute aggravation in clinical state that is reversible after parenteral administration of a glucocorticoid.

2. Epidemiology

2.1. Adults

The incidence of acute adrenal insufficiency is estimated to be 6–8.3 episodes/100 patients/yr \cite{[1,2,4]} and increases with age \cite{[5]}. It is a complication of both primary adrenal insufficiency and corticotropin (ACTH) insufficiency \cite{[1,2]}. It is a serious condition that is linked to increased mortality, being the cause of death in 6–15\% of cases in patient with adrenal insufficiency \cite{[6–8]}. In a prospective study by Hahner et al. \cite{[4]}, mortality linked to an episode of acute adrenal insufficiency was 0.5/100 patients/yr. Primary adrenal insufficiency, female gender, associated comorbidities (diabetes, asthma) and diabetes insipidus are risk factors that have been described in retrospective studies \cite{[1,2,9]}. Previous episodes of acute adrenal insufficiency was the only risk factor identified in a recent prospective study [odds ratio 2.9, 95\% confidence interval (CI), 1.5–5.5] suggesting that individual susceptibility varies from one patient to another \cite{[4]}.

2.2. Children

A single retrospective study has looked at the risk of acute adrenal insufficiency in relation to the cause of chronic adrenal insufficiency. It showed that the number of pediatric hospitalizations for acute adrenal insufficiency was higher in primary adrenal insufficiency cases than those with ACTH insufficiency. Congenital adrenal hyperplasia (CAH) corresponds to approximately half of the adrenal crises due to primary adrenal
insufficiency. There was no gender difference observed for emergency hospitalizations, regardless of the cause of adrenal insufficiency [10]. A recent prospective study in a pediatric population with congenital adrenal hyperplasia found an incidence of acute adrenal insufficiency in the first 6 years of life to be 6.5/100 patients/yr (27.5% of patients, all with salt loss), most often caused by an episode of infection and poor treatment adaptation by their carers/parents. Conversely, episodes of hypoglycemia were not found to have causal or contributing factors [11].

3. Causal factors

3.1. Adults

Digestive problems (vomiting, diarrhea) are the factors most frequently reported as triggering acute adrenal insufficiency (33–59%) [1,2]. However, these are equally signs of adrenal crisis, leading to an overestimate of their frequency as causal factors [5]. Bacterial or viral infections (infectious lung diseases, urinary tract infections, septicemia, flu-like syndrome) represent the second most common causes of acute adrenal insufficiency (17–24%). In a prospective study on 423 patients followed over 2 years [4], 46 patients presented with acute adrenal insufficiency. Major work or personal/family stress was identified as a triggering factor in 30% of cases, that is, as frequently as digestive troubles or infections (35% and 32%, respectively). Other factors that were reported included surgery, trauma, severe pain (infarct, severe migraine), delivery, intense sustained physical exercise and heat were also reported to trigger adrenal crisis. Stopping or repeatedly forgetting to take hydrocortisone treatment were the cause of 11% of adrenal crises in some studies [2]. Introduction of diuretic treatment, a low sodium diet or chemotherapy resulting in digestive troubles, can also result in adrenal crisis. Hemorrhage, severe allergic reactions and acute alcohol intoxication were more rarely reported as factors. Failure to increase the dose of hydrocortisone when introducing a treatment that can modify hydrocortisone metabolism (enzyme inducers: phenobarbital, phenytoin, carbamazepine, rifampicine, mitotane) or introduction of a treatment that reduces hydrocortisone absorption (resins, exenatide) are also possible triggering factors. In 1–7% of cases reported, the cause was not identified [1,2].

3.2. Children

The causes of adrenal crisis are principally gastrointestinal infections. Specifically, in the case of congenital adrenal hyperplasia, the causes of adrenal crisis are, in order of frequency, gastrointestinal infections, respiratory infections and other febrile infections. Crises may arise specifically in the first year of life in cases of infectious lung disease or urinary tract infections, particularly in girls undergoing genital reconstructive surgery for reflux [12]. In the case of primary adrenal insufficiency and particularly in congenital adrenal hyperplasia, the absence of an identified triggering factor is frequently noted.

4. Diagnosis of acute adrenal insufficiency

4.1. Adult patients

4.1.1. Clinical signs

Clinical signs are specific and, for some signs, shared with the triggering factor [13–17]. The appearance of clinical signs is usually rapid, over a period of hours [18]. The median time between manifestation of the first signs and adrenal crisis is approximately 24 hr. The signs most frequently observed are:

- asthenia, often major fatigue, inertia or lack of energy, fatigue, drowsiness, or on the contrary, confusion and agitation that can evolve into loss of consciousness and even coma in the absence of suitable treatment;
- anorexia, nausea, vomiting, diarrhea, diffuse abdominal pains;
- hypotension, postural hypotension, tachycardia, general dehydration;
- pallor, sweating;
- hyperthermia;
- cramps, pseudoparalysis;
- acute circulatory insufficiency resulting from hypovolemia and a vasopregia resistant to vasoconstrictor amines (reduction in synthesis or membrane expression of α- and β-adrenoceptors secondary to the glucocorticoid deficiency).

In acute ACTH insufficiency, hypovolemia is not normally observed except in cases with serious digestive problems.

4.1.2. General biochemical signs

Hyponatremia is a consequence of sodium loss due to the deficiency in mineralocorticoids in primary adrenal insufficiency but also due to hemodilution secondary to increased secretion of arginine vasopressin (AVP), the principal mechanism in ACTH insufficiency (reduction in the osmolality threshold stimulating AVP secretion secondary to the deficiency in glucocorticoids) [19]. The mineralocorticoid deficiency explains the hyperkalemia observed in primary adrenal insufficiency. Metabolic acidosis is also frequently seen. Functional renal insufficiency is a consequence of hypovolemia, Normocytic normochromic anemia, lymphocytosis, eosinophilia and a moderate increase in plasma calcium may also be observed. These biological and biochemical signs are not constant however [20].

In the case of adrenal crisis in ACTH insufficiency, hyperkalemia is not observed. Hypoglycemia is more frequently found in cases of associated somatropin insufficiency.

4.1.3. Hormone assays

Diagnosis is based on clinical signs, supported by results of standard biochemical tests where the adrenal insufficiency was known prior to the acute episode. Diagnosis can be difficult if the deficiency is partial or is acutely manifested (bilateral adrenal hemorrhage, pituitary adenoma apoplexy). Acute adrenal insufficiency should be suspected in all cases of unexplained acute circulatory failure with hyponatremia (with or without hyperkalemia). A blood sample should be taken immediately for
cortisol assay and treatment should be started without waiting for assay results.

Diagnosis is confirmed if the plasma cortisol is lower than 5 μg/dL (50 ng/mL, 138 nmol/L). Measurement of ACTH should allow diagnosis of primary adrenal insufficiency (increased ACTH) or of ACTH insufficiency (ACTH normal or low). If plasma cortisol is between 5 and 18 μg/dL (50 ng/mL and 180 ng/mL, 138 nmol/L and 490 nmol/L) (not adapted for the acute situation) treatment with hydrocortisone is followed and dynamic diagnostic tests carried out after the acute episode (Synacthen™ test, Insulin Hypoglycemia test) (see Chapter 2, Diagnosis of adrenal insufficiency, Ann Endocrinol 2017).

An improvement after administration of parenteral hydrocortisone hemisuccinate is the best diagnostic criterion.

4.2. Pediatric patients

There is little published data concerning methods of detecting acute adrenal insufficiency in pediatric patients. From the available publications, an analysis based on distinguishing between acute adrenal insufficiency arising in patients with congenital adrenal hyperplasia, those arising where there are other causes of primary adrenal insufficiency, and those in ACTH insufficiency could be suggested.

4.2.1. General clinical and biochemical signs

The clinical signs that show primary adrenal insufficiency in children are, as in adults, non-specific and can be confounded with the triggering factor. Classically, asthenia, nausea, vomiting and abdominal pains are seen. More specific signs of glucocorticoid deficiency are signs of hypoglycemia (pallor, sweating, disorientation, mood change). Mineralocorticoid deficiency can be responsible for hypotension, tachycardia, dehydration, vertigo, loss of weight and salt craving [21,22].

4.2.2. In cases of known congenital adrenal hyperplasia

A published study of children presenting with congenital adrenal hyperplasia provides information on the frequency of acute adrenal crises and their clinical and biochemical manifestations [12]. In a retrospective study looking at adrenal crises over the lifetime of patients, the median age when adrenal crisis arose was 4.5 yr. The majority of crises arose before the age of 10 yr. Symptoms were, in order of frequency: nausea, vomiting, fever, dehydration, diarrhea, fatigue and abdominal pain. The biochemical anomalies found were, in order of frequency: hyponatremia, hyperkalemia and metabolic acidosis.

4.2.3. Conditions other than congenital adrenal hyperplasia

A published study has described the symptoms at diagnosis in a series of 18 patients. These were digestive problems (nausea, vomiting; 16/18 cases), hypotension (13/18 cases), hyperpigmentation (12/18 cases), hyponatremia (<135 nmol/L; 16/18 cases), Hyperkalemia was less frequent (>5 mmol/L; 9/18 cases) as was hypoglycemia (4/15 cases) [23]. In a series of children presenting with primary adrenal insufficiency where the diagnosis in 4 patients was acute adrenal insufficiency, none presented with hyperkalemia [24]. Thus, if hyponatremia is found in most cases of acute adrenal insufficiency, regardless of the origin of the pathology, hyperkalemia appears to be more frequent in congenital adrenal hyperplasia than in other causes of primary adrenal insufficiency in children.

4.2.4. In known cases of ACTH insufficiency

One publication describes adrenal crisis in cases of diagnosed ACTH insufficiency undergoing treatment. Severe hypoglycemia accompanied by changes in consciousness or convulsions are the most frequent signs of adrenal crisis, particularly in children under 5 years of age. These children present without abnormal potassium levels [18]. In neonates, diagnosis is most frequently suggested by convulsions, secondary to hypoglycemia.

4.2.5. Special cases of relative adrenal insufficiency in premature infants in intensive care

The diagnosis of relative adrenal insufficiency is suggested by shock that is resistant to treatment with volume support and vaspressors [25,26].

4.2.6. Hormone assays

Same as in the adult for positive diagnosis of adrenal insufficiency (see 3.1.3).

5. Treatment of acute adrenal insufficiency

Adrenal crisis represents a medical emergency. If acute adrenal insufficiency is suspected, in both adults and children, treatment should be by immediate parenteral hydrocortisone hemisuccinate, correction of electrolyte imbalance and, if necessary, treatment of hypovolemia. Additionally, treatment of hypoglycemia and treatment of the cause of the adrenal crisis may be required. Treatment should be started urgently, after assays for cortisol and ACTH if the diagnosis of adrenal insufficiency was not already known, but without waiting for assay results. In case of hydrocortisone being unavailable, prednisolone may be used.

5.1. In the adult patient

Injection of a 100 mg bolus of hydrocortisone hemisuccinate intravenously (IV) or intramuscularly (IM), should immediately be followed by administration of hydrocortisone hemisuccinate ideally by continuous IV infusion (see Table 1). Otherwise, bolus injections, either IV or IM, should be administered every 6 hr. Recommended doses reported in the literature vary from 100–300 mg/24 hr [27–29]. There is no data suggesting benefit from a dose greater than 100 mg/24 hr when delivered by continuous IV infusion. Treatment for the cause of the adrenal crisis should be added, if appropriate, as well as prevention of thromboembolism and administration of proton pump inhibitors to prevent possible gastric stress ulceration. In primary adrenal
5.2. In the pediatric patient

In this section, we address the condition in pediatric patients specifically and their therapy.

The dose of parenteral hydrocortisone hemisuccinate delivered by injection suggested by experts, with different doses advised by different authors:

Table 1
European and US recommendations for the prevention of acute adrenal insufficiency in adults.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Husebye 2014 [27]</th>
<th>Bornstein 2016 [29]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgery</td>
<td>100 mg hydrocortisone hemisuccinate via IM injection just prior to anesthesia then 100 mg IM every 6 hr until patient returns to eating (at least 24–48 hr). On return to oral treatment, double the dose during the first 24–48 hr (depending on clinical state) then a progressive return to normal doses</td>
<td>100 mg hydrocortisone hemisuccinate via IV infusion then 200 mg/24 hr as continuous IV infusion (or bolus IV or IM injections of 50 mg/6 hr). Rapid reduction in the dose and return to oral administration depending on the change in clinical state</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>100 mg hydrocortisone hemisuccinate by IM injection of continuous infusion throughout the surgical intervention. Followed by return to oral administration with double the normal dose during the first 24 hr</td>
<td>Hydrocortisone, 25–75 mg/24 hr for 1–2 days</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Increase in the dose of hydrocortisone in the third trimester of pregnancy from 2.5 to 10 mg/day ± increased dose of mineralocorticoid (depending on blood pressure and plasma ion measures)</td>
<td>Increase in the dose of hydrocortisone by 20–40% from 24th week after last menses, normally 5–10 mg Increase in mineralocorticoid dose is rarely necessary</td>
</tr>
<tr>
<td>Delivery</td>
<td>100 mg hydrocortisone hemisuccinate by IM injection at the start of labor followed by doubling the oral dose during 24–48 hr, then a progressive return to normal dose</td>
<td>100 mg hydrocortisone hemisuccinate by IV infusion at the start of labor then administration of 200 mg/24 hr by continuous IV infusion during active labor (cervical dilation &gt; 4 cm and/or contractions every 5 min). Double the oral dose during the next 24–48 hr and then a progressive return to normal dosage</td>
</tr>
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</table>

R5-1: In adults, we recommend injection of hydrocortisone hemisuccinate 100 mg by IM or IV route followed immediately by IV infusion of 100 mg/24 hr by syringe pump (alternatively, bolus injection IV or IM of 25 mg each 6 hr). Treatment needs to be commenced urgently, after assay for cortisol and ACTH if the diagnosis of adrenal insufficiency was not previously known, and without waiting for results.

After correction of clinical and fluid balance problems, we recommend a return to oral administration of hydrocortisone, tripling the normal dose (at least 60 mg/24 hr in patients normally treated with low-dose), taken as 3 doses across the day (morning, midday, and evening). Return to normal dose should then be by progressive reduction of the dose over several days.

In patients with primary adrenal insufficiency, treatment with fludrocortisone should not be recommended until the hydrocortisone dose is less than 50 mg/day.

Strong recommendation. Expert opinion.

R5-2: In adults, with primary adrenal insufficiency, we recommend administration of one liter of isotonic saline in the first hour. The speed of infusion and the volume of isotonic saline (with 10% glucose in cases of hypoglycemia) administered should be modified according to clinical and hemodynamic surveillance of the patient. Treatment should be maintained for 24–48 hr. In ACTH insufficiency, treatment should also include IV infusion to correct fluid and electrolyte loss. Isotonic saline is administered only in cases of digestive problems and/or hypotension.

Strong recommendation. Expert opinion.

- Bornstein et al. [29] (consensus 2016): injection of hydrocortisone hemisuccinate at 50–100 mg/m² followed by a daily dose of 50–100 mg/m²/day (administered every 6 hr);
- Shulman et al. [22]: injection of hydrocortisone hemisuccinate at 50–75 mg/m²/day, administered every 6 hr;
- PNDS (National Care Plan) for congenital adrenal hyperplasia 2011 [30]: injection of hydrocortisone hemisuccinate at 2 mg/kg every 4–6 hr in IV drip or every 6–8 hr by IM injection, depending on clinical state.

Since hydrocortisone hemisuccinate is usually used in conjunction with IV rehydration (with saline) there is generally no need for mineralocorticoids to be administered.

6. Prevention of acute adrenal insufficiency

It is necessary to increase the provision of hydrocortisone in situations likely to lead to adrenal crisis in patients with adrenal insufficiency. There is, however, little published data on the synthesis and concentration of cortisol in such situations in normal subjects. There are no randomized controlled


R5-3: Pediatric patients
We recommend:

- administration of injectable hydrocortisone hemisuccinate (100 mg ampoule) 2 mg/kg/6 hr in IV drip or each 6–8 hr via IM or SC injection;
- parenteral rehydration using 5% glucose or 10% glucose in cases of hypoglycemia with provision of NaCl of 10–15 mEq/kg/day (maximum 408 mEq/day = 24 g, plasma sodium must not increase by more than 1 mEq/kg/hr) and provision of fluids according to the age of the patient: newborn: 150–180 mL/kg/day; child: 2.5–3 L/m²/day. Volume replacement with isotonic saline in case of circulatory collapse (10–20 mL/kg) is sometimes necessary.

Clinical surveillance (monitor, blood pressure, heart rate, glycemia, urine output, weight, alertness) and biochemical surveillance, adapted for fluid and electrolytes and the speed of their correction, is essential.

Strong recommendation. Expert opinion.

6.1. During surgical intervention

Udelsman et al. [31] looked at surgical stress by carrying out cholecystectomy on monkeys with bilateral adrenalectomy and showed that the outcome did not differ between animals that were treated with either physiological levels of hydrocortisone and those who received 10 times normal doses of hydrocortisone. They described an increase in mortality and more hemodynamic disturbance only in animals that received a tenth of the normal replacement dose. Studies in human subjects examining the rate of production of cortisol during surgical intervention are historical and describe small numbers of subjects [32–35]. They report levels between 60 mg and 220 mg/24 hr depending on the severity and duration of the operation, leading the authors to distinguish between minor surgery (carried out under local anesthetic or of < 1 hr duration), medium (hysterectomy via laparotomy, partial colectomy, installation of articular prosthesis, cholecystectomy, revascularization of the lower limb) or major (procto-colectomy, duodeno-pancreatectomy, esophagectomy, gastrectomy, thoracotomy, cardiac surgery). The rate of cortisol production rarely exceeds 200 mg/day during major surgery.

Salem et al. [36] proposed delivery of 25 mg/day in the case of minor surgery, 50–75 mg/day during one or two days for medium surgery and 100–150 mg/day over 2 or 3 days in the case of major surgery. The recommendations of the European Endocrine Society [27] and the American Endocrine Society [29] are summarized in Table 1, proposing higher doses of hydrocortisone. The results of two recent studies on pharmacokinetics nevertheless suggest that lower doses are sufficient. After IV injection of 50 mg hydrocortisone the peak cortisol is high (88 ± 13 μg/dL), reached 30 min after the injection and varies between subjects. The concentration of cortisol remains within the range 14.4 to 32 μg/dL in more than 88% of healthy subjects studied 5 hr after injection [37]. After IM injection of 100 mg, the mean peak cortisol is 110 ± 29 μg/dL, observed 66 ± 51 min after injection. The plasma concentration of cortisol was still higher than 50 μg/dL, 4 hr after injection [38].

R5-4: In adults we suggest on the day of surgery or intervention, an IM or IV injection of a 100 mg bolus of hydrocortisone hemisuccinate, followed in the case of major surgery, by continuous infusion of hydrocortisone hemisuccinate, 100 mg/24 h (or alternatively 25 mg IM or IV every 6 hr), to be continued until patients return to eating. On return to oral treatment, normal dose should be tripled (at least 60 mg/day), taken three times per day (morning, midday and evening) before gradual reduction of the dose over a few days to the normal dose. In primary adrenal insufficiency, treatment with fludrocortisone should be recommenced when the hydrocortisone dose has been reduced to < 50 mg/day.

Weak recommendation. Expert opinion.

R5-5: In children, we suggest that on the day of the intervention the same protocol as that used in cases of acute adrenal insufficiency be employed, and continued until the patient returns to eating. When oral treatment is recommenced, the normal dose of hydrocortisone should be tripled and taken in three administrations per day (morning, midday and evening) before progressively reducing the dose over several days to the normal dose. In cases of light anesthesia, minor surgery or examination that requires fasting conditions, we suggest hydrocortisone hemisuccinate 2 mg/kg/4–6 hr by IV injection or each 6–8 hr by IM injection, to be continued if the fasting state continues, and after to return to normal oral hydrocortisone administration.

Weak recommendation. Expert opinion.

6.2. During pregnancy and childbirth

Production of cortisol and ACTH progressively increase during gestation [39,40]. Plasma free cortisol concentrations show
a mean increase of 60% in the third trimester of pregnancy with a large variation between women [40]. Several factors play a role: an increase in transcortin, modification of negative feedback of glucocorticoids on pituitary ACTH secretion [41,42], placental secretion of CRH and ACTH [43] and increased adrenal sensitivity to ACTH [44]. Pregnancy is also characterized by an increased activation of the renin-angiotensin-aldosterone system.

Digestive problems in the first trimester of pregnancy lead to a recommendation to deliver parenteral hydrocortisone in this situation. Increased hydrocortisone treatment in the second trimester is possible, essentially guided by clinical observation and data. It is generally unnecessary to increase mineralocorticoid treatment during pregnancy [39,43]. However, possible signs of overdose of hydrocortisone (weight gain, striae) or conversely, under-dosage (fatigue, nausea) are not specific and are often observed during normal pregnancy. Thus, provision of hydrocortisone is not always required [39].

At the time of parturition, plasma concentrations of ACTH are 10 times greater than those observed in non-pregnant women [46] and concentrations are higher during vaginal delivery compared to caesarean delivery [47], suggesting that childbirth is equivalent in stress to that of major surgical procedures.

Lindsay and Nieman [39] recommended doubling the normal dose of hydrocortisone during labor if oral administration was well-tolerated, or the IM or IV injection of 50 mg hydrocortisone during labor, repeated if necessary depending on the duration of labor. In the case of caesarean delivery, IM or IV injection of 100 mg hydrocortisone hemisuccinate just prior to surgery is recommended, re-administered as 25 mg injections every 6–8 hr after birth and up to the patient taking food. Return to normal dose by oral administration should be then 24–48 hr later. Lébée et al. [45] suggested administration of higher parenteral doses of hydrocortisone (50–100 mg by IM or IV injection every 6–8 hr from the start of the active phase of labor or continuous infusion of 200–300 mg/24 hr) up to delivery.

The European recommendations are summarized in Table 1.

6.3. During colonoscopy

Acute adrenal insufficiency has been observed in patients undergoing colonoscopy [48,49]. Husebye et al. [27] proposed hospitalizing patients the day before colonoscopy and the administration of 100 mg hydrocortisone hemisuccinate by IM injection at the start of digestive preparation with additionally IV infusion of isotonic saline or isotonic glucose. The injection of hydrocortisone hemisuccinate is then repeated just prior to colonoscopy. They also recommended the doubling of oral hydrocortisone treatment in the 24 hr following the procedure.

6.4. In patients hospitalized with an acute intercurrent illness

Plasma cortisol concentrations are increased in patients who are in intensive care [50–54]. The increased level varies depending on the nature and severity of the condition. In the study by Michalacki et al. [53], cortisol levels were significantly elevated in patients hospitalized due to stroke (24 ± 9 µg/dL) or severe sepsis (38 ± 25 mg/dL) when compared to control subjects (13 ± 6 µg/dL). Small increases in cortisol levels in patients hospitalized for respiratory or urinary tract infection were not significant. Plasma concentrations of cortisol at 2 am are on
average higher than 10 μg/dL in the three groups of patients with abnormal cortisol secretion but diurnal rhythm of secretion is abolished only in patients suffering from stroke or severe sepsis.

This increase in cortisol levels is dissociated from ACTH secretion, which is normal [44] or reduced [55,56]. In a study of 158 patients in intensive care, Boonen et al. [55] showed that the increase in cortisol levels (3.5×) is a consequence of increased cortisol production (by 83%) but equally of a more than 50% reduction in metabolic clearance, suggesting that the doses of hydrocortisone classically recommended in these patients (200 mg/24 hr) are excessive.

6.5. Education of patients and/or parents and general practitioners in acute adrenal insufficiency (also see Chapter 6. Monitoring and therapeutic education)

Acute adrenal insufficiency is often the consequence of the lack of adaptation by the patient or by their general practitioner to an acute situation. Prevention relies therefore on education of the patient and/or parent, in the case of pediatric patients, and their general practitioner. A card with information on the condition, the glucocorticoid and mineralocorticoid treatments prescribed and the clinicians responsible for monitoring should be given to the patient, to be kept with their identity papers (emergency care card “adrenal insufficiency”). The importance of normal dietary sodium intake and the prevention of dehydration should also be explained to the patient. The patient must be informed of the necessity to increase the dose of hydrocortisone themselves in case of infection, traumatic stress or psychological stress (60 mg/day in adults, double or triple doses in pediatric patients, taken in three doses across the day, i.e. morning, midday and evening), or in the case of sustained intense physical exercise 5–10 mg before commencing. The increase in oral dose is however, not always sufficient to avoid adrenal crisis [5,18].

In the absence of an improvement in clinical symptoms after increasing oral treatment, an injection of 100 mg hydrocortisone hemisuccinate must be administered. This can be performed by nursing staff as an IM injection or as a SC injection by the patient himself or a carer/family member. Hahner et al. [38] showed that the peak in cortisol concentration is comparable after either IM or SC injection (97 ± 28 μg/dL vs. 110 ± 29 μg/dL). The time between injection and peak concentration is moderately slower in the case of SC injection (91 ± 34 min vs. 66 ± 51 min) as is the time taken to obtain a concentration of >36 μg/dL (22 ± 11 vs. 11 ± 5 min), however, the difference is less than the wait involved in contacting a health professional and obtaining an IM injection. The patient and his family members or carers therefore need to be educated in administering hydrocortisone hemisuccinate by self-injection. In case of vomiting, the patient needs to be informed of the need to re-administer hydrocortisone, regardless of the time of day, 20 mg hydrocortisone in adults and double or triple dose in children. If there is repeated vomiting parenteral hydrocortisone hemisuccinate should be administered by IM or SC injection (100 mg in adults or adolescents, 2 mg/kg in children). After self-administering the injection, the patient should then contact his physician. Vials of hydrocortisone hemisuccinate, syringes and needles for performing the injections need to be prescribed for the patient who also needs to verify the expiry dates of drugs and material that are stored. The patient needs to always have with himself the necessary materials for injecting a vial of hydrocortisone hemisuccinate since a third of adrenal crises occur when the patient is away from home [2].
R5-10: We recommend:

- that all patients are given a card identifying them as requiring urgent medical care, marked “adrenal insufficiency”;
- that patients and parents of pediatric patients be educated as to the risks of adrenal insufficiency, how to increase the dose of hydrocortisone themselves in cases of stress, infection, trauma and how to adapt their treatment to altered circumstances (heat, physical exercise, travel);
- patients and their family/carers should be educated in how to perform SC injections of hydrocortisone hemisuccinate;
- all patients should be provided with prescriptions for 100 mg ampoules of hydrocortisone hemisuccinate and syringes and needles for preparation and delivery of the injection. The patient always needs to carry the necessary materials for injection with them;
- there should be regular evaluation of patient knowledge, as well as that of their family/carers and their physician, about their condition.

Strong recommendations. Expert opinion.

Disclosure of interest

The authors declare that they have no competing interest.

References


