EXTENSIVE EXPERTISE IN ENDOCRINOLOGY

Adrenal crisis

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Abstract

Adrenal crisis is a life-threatening emergency contributing to the excess mortality of patients with adrenal insufficiency. Studies in patients on chronic replacement therapy for adrenal insufficiency have revealed an incidence of 5–10 adrenal crises/100 patient years and suggested a mortality rate from adrenal crisis of 0.5/100 patient years. Patients with adrenal crisis typically present with profoundly impaired well-being, hypotension, nausea and vomiting, and fever responding well to parenteral hydrocortisone administration. Infections are the major precipitating causes of adrenal crisis. Lack of increased cortisol concentrations during infection enhances pro-inflammatory cytokine release and sensitivity to the toxic effects of these cytokines (e.g. tumour necrosis factor alpha). Furthermore, pro-inflammatory cytokines may impair glucocorticoid receptor function aggravating glucocorticoid deficiency. Treatment of adrenal crisis is simple and highly effective consisting of i.v. hydrocortisone (initial bolus of 100 mg followed by 200 mg over 24 h as continuous infusion) and 0.9% saline (1000 ml within the first hour). Prevention of adrenal crisis requires appropriate hydrocortisone dose adjustments to stressful medical procedures (e.g. major surgery) and other stressful events (e.g. infection). Patient education is a key for such dose adjustments but current education concepts are not sufficiently effective. Thus, improved education strategies are needed. Every patient should carry an emergency card and should be provided with an emergency kit for parenteral hydrocortisone self-administration. A hydrocortisone pen would hold a great potential to lower the current barriers to hydrocortisone self-injection. Improved patient education and measures to facilitate parenteral hydrocortisone self-administration in impending crisis are expected to significantly reduce morbidity and mortality from adrenal crisis.

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Introduction

This narrative review on adrenal crisis is based on personal experience, own research, and comprehensive evaluation of the literature. It aims at contributing to more effectively combat morbidity and mortality from adrenal crisis.

Being the first to diagnose and treat adrenal insufficiency in a patient, after months of suffering with a multitude of futile investigations, is a most rewarding experience for any endocrinologist. Usually within 24 h

Invited Author's profile

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after initiation of treatment, improvement in well-being is profound and often experienced by the patient as a miracle. This initial tremendous improvement in well-being has deceived expert physicians for some decades and led them to believe that treated patients with adrenal insufficiency lead a largely normal life with a normal life expectancy (1, 2, 3). Only in recent years, it became evident that restoration of well-being remains incomplete (4, 5, 6, 7, 8, 9). The reasons for this incomplete recovery of well-being with current replacement regimens are still not fully understood and comprise among others a non-physiological glucocorticoid replacement with an altered diurnal rhythm of cortisol availability (10, 11, 12, 13, 14), lack of DHEA (15, 16, 17) and reduced adrenaline secretion from the adrenal medulla (18, 19). Even more recent is the discovery that mortality is also increased in patients with chronic adrenal insufficiency receiving standard replacement therapy (20, 21). This also affects patients with secondary adrenal insufficiency (22, 23, 24). The more than twofold increased standardised mortality ratio in primary adrenal insufficiency is mainly due to cardiovascular causes and infections (20, 21).

Most importantly, adrenal crisis also contributes to excess mortality in patients with diagnosed chronic adrenal insufficiency. Adrenal insufficiency accounted for 15% of deaths in a Norwegian study of 130 deceased patients with Addison's disease, most probably reflecting the adrenal crisis (25). Two Swedish registry analyses in patients with Addison's disease reported 'endocrine causes' as responsible for the death in 12.6 and 8.3%, respectively, also suggesting a role of adrenal crisis (20, 21). Similarly, among 1286 Swedish patients with hypopituitarism, adrenal crisis in response to acute stress and intercurrent illness was identified as an important cause of excess mortality (24).

Studies on the epidemiology of adrenal crisis give a consistent picture with an incidence between five and ten adrenal crises per 100 patient years in patients on standard replacement therapy. In a retrospective analysis of 444 patients with primary or secondary adrenal insufficiency, we observed a frequency of 6.3 adrenal crises/100 patient years (26). Reisch *et al.* (27) studied the incidence in adult patients with congenital adrenal hyperplasia and reported a frequency of 5.7 crises/100 patient years. More recently, Ritzel *et al.* (28) have investigated patients after bilateral adrenalectomy for Cushing's syndrome and found 9.3 crises/100 patient years. The largest analysis thus far was conducted via a postal survey by the UK Addison's disease Self Help Group in 841 patients from the UK, Canada,

Australia, and New Zealand indicating an incidence of eight crises per 100 patient years (29). However, these were all retrospective studies susceptible to various biases. In the first prospective study (30), we have recently observed 64 adrenal crises in 767.5 patient years (8.3 crises/100 patient years). Thus, approximately one in 12 patients will experience a life-threatening crisis in the coming year. This is a substantial percentage. Notably, there is an uneven distribution in the occurrence of crises, as some patients do not experience a single adrenal crisis for decades, while others have recurrent adrenal crises (26, 29). The reasons for this variability in crisis susceptibility are not understood.

Importantly, in this first prospective study, four patients died from adrenal crisis during 2 years of follow-up leading to a mortality rate from crisis of 0.5/100 patient years. If confirmed in future studies, this would indicate an unacceptable death toll from adrenal crisis, as this condition is eminently treatable. Assuming a prevalence of adrenal insufficiency of 2.18–4.20/10 000 population (31) and a population of 507 million in the European Union (EU) (www.ec.europa.eu/eurostat), adrenal insufficiency affects between 110 526 and 212 940 people in the EU, leading to 5526 to 10 647 expected deaths from adrenal crises in the coming decade in the EU, if the current situation prevails.

A prismatic case

A 40-year-old male with autoimmune Addison's disease on stable replacement therapy for 20 years developed diarrhoea and vomiting. His young daughters had recently suffered from gastroenteritis, which had been attributed to a Noro virus infection detected in their day care. The patient increased his oral dose of hydrocortisone, but his general health had markedly deteriorated the following day. His wife urged him to ask for professional help, but he declined indicating that he could manage the problem himself. He again increased his oral hydrocortisone dose. The following day there was evidence of cardiovascular failure and his wife called for emergency help. At arrival in hospital, the patient had no measurable blood pressure. Resuscitation was immediately started together with administration of i.v. hydrocortisone and rehydration. After transient stabilisation, cardiopulmonary resuscitation eventually remained unsuccessful and the patient died from adrenal crisis. Reportedly, one of his daughters later told her peers that she was responsible for the death of her father, as she had brought the infection to the family.

A number of lessons can be derived from this case: gastroenteritis is a particular dangerous cause of adrenal crisis, oral hydrocortisone is frequently insufficient to reverse impending adrenal crisis, current education of patients is often not sufficiently effective, unwillingness to call for help (according to the patient's wife a feature of his personality) carries a huge risk and, at a certain point in time, damage from adrenal crisis will become irreversible no longer responding to medical measures. Finally, such an event is likely to have a life-long detrimental impact on the well-being of affected families.

This death in one of our patients, who had received repeated education during his outpatient visits and detailed written information concerning his disease, clearly also had an impact on my attitude to crisis prevention: I concluded that more effective efforts are needed to successfully combat such easily preventable mortality from adrenal crisis!

Clinical presentation

Patients with adrenal crisis typically present with severe hypotension and clinical evidence of hypovolaemia. Cardiovascular evaluation may find an abnormal electrocardiogram or even evidence of cardiomyopathy (32, 33, 34, 35). Patients often appear exhausted and depressed. They report fatigue and a profound lack of energy. Adrenal crisis is often associated with anorexia, nausea, and vomiting (26, 29), frequently misinterpreted as evidence of gastrointestinal disease (36). Even more so, patients may complain of abdominal pain suggestive of early peritonitis (37). Fever is frequently observed, as in many instances adrenal crisis is triggered by infection. However, fever may also present as fever of unknown origin (38). At a later stage, patients can develop impaired cognition and somnolence (36).

In patients with undiagnosed adrenal insufficiency, there is usually a history of steadily declining general health over weeks to months or even over years with increasing fatigue, anorexia and weight loss. Patients with primary adrenal insufficiency develop the characteristic increased pigmentation related to hypersecretion of proopiomelanocortin-derived peptides, which may guide the diagnosis (31). A substantial subset of patients is diagnosed with psychiatric illness, in particular with anorexia nervosa (36, 39). Most patients have undergone extensive and repeated clinical investigations including endoscopy and imaging. Acute decompensation to full-blown crisis is then eventually triggered by a stressful event (e.g. surgery or infection).

A number of studies have investigated the causes of adrenal crisis in patients with already diagnosed chronic adrenal insufficiency (26, 27, 28, 29, 40). Again infections, particularly gastroenteritis, are the most frequent causes. In addition, surgery, strenuous exercise, emotional stress and accidents contribute to adrenal insufficiency (29, 30). Notably, cessation of glucocorticoid therapy by the patient (or by the attending physician) may also precipitate adrenal crisis. In a recent study, in ~10% of crises, patients were unable to identify a clear cause (30).

In my experience, development of an adrenal crisis usually takes several hours. However, there is substantial variation and a friend of mine who is an experienced paediatric endocrinologist insisted that, in children, adrenal crisis often develops very rapidly (Wolfgang Sippell, personal communication). Moreover, hypoglycaemia seems to be more common in children than in adults (41, 42). An orthopaedic colleague with longstanding adrenal insufficiency also confirmed that his adrenal crises occasionally evolved within an hour making it quite difficult for him to take the necessary preventive actions. In a survey of 37 patients who had experienced an adrenal crisis in the context of a prospective study (43), the median time from first symptoms to contacting health professionals was 135 min (range 5 min to 7 days) (unpublished data).

Definition of adrenal crisis

When we planned a prospective study on the incidence of adrenal crisis in patients with known adrenal insufficiency, we realised the need to define what actually constitutes an adrenal crisis. However, we found neither a textbook nor a paper providing such a definition, leaving us with the task to generate our own definition. We then decided to define adrenal crisis as a profound impairment of general health and at least two of the following conditions: hypotension (systolic blood pressure <100 mmHg), nausea or vomiting, severe fatigue, hyponatraemia, hypoglycaemia and hyperkalaemia, triggering subsequent parenteral glucocorticoid administration. However, it turned out that in our prospective study hyponatraemia or hyperkalaemia contributed very little to the case finding.

Furthermore, we introduced a grading system depending on the setting required for treatment (grade 1: outpatient setting; grade 2: in hospital care on a general ward; grade 3: admission to an intensive care unit); and outcome (grade 4: death from adrenal crisis).

This definition clearly is debatable. In particular, it may also be important to include the reversal of symptoms

after administration of glucocorticoids. For example, one of my patients (adrenalectomised for a metastatic adrenocorticotrophin-secreting neuroendocrine tumour) showed no improvement in his severely impaired health and hypotension after i.v. glucocorticoid administration. He was later diagnosed with intestinal perforation. Thus, a slightly modified definition is given in Table 1. I believe that this definition is highly useful and can serve as a pragmatic tool for future prospective investigations.

Physiopathology of adrenal crisis

The physiopathology of adrenal crisis is only partially understood. Hypotension can be explained by a lack of the permissive action of glucocorticoids on adrenergic receptors (44, 45, 46, 47) and by volume depletion caused by a lack of sodium and fluid retention due to missing mineralocorticoid activity (31, 48). Volume depletion may further be worsened by vomiting and diarrhoea.

It is well known that fever and infection lead to an increase in circulating cortisol levels in healthy subjects and, therefore, it is generally recommended that such an increase in cortisol levels should be mimicked by adjustment of the hydrocortisone dose in patients with adrenal insufficiency (31, 49). This course of action is a well-accepted standard of care, but the underlying mechanisms necessitating it are less clear. It has been proposed that glucocorticoids influence stress response by permissive, suppressive, stimulatory, and preparative actions (47). While a lack of permissive action of glucocorticoids is highly likely in patients with undiagnosed adrenal insufficiency leading to impaired activation

and responsiveness of the cardiovascular system, it is expected that adequate stable replacement therapy for chronic adrenal insufficiency ensures sufficient glucocorticoid activity for permissive action providing, for example, sufficient sensitivity to catecholamines during stress (50, 51). Thus, in patients with known adrenal insufficiency, the permissive action that is lacking is probably less, but the suppressive activity of increased glucocorticoid secretion is missing in adrenal crisis. This suppressive activity prevents the harmful effects of an overshooting immune defence (52, 53), probably primarily mediated via pro-inflammatory cytokines (47). Infection triggers the release of cytokines such as interleukin 1 (IL1), tumour necrosis factor alpha (TNF α) and interleukin 6 (IL6), which physiologically stimulate the hypothalamus–pituitary–adrenal (HPA) axis leading to increased cortisol concentrations (54, 55). In turn, high glucocorticoid levels diminish cytokine release and action preventing their potential detrimental effects (56, 57). Accordingly, cytokines are increased in adrenalectomised experimental animals and doses of TNF α or IL1, which are readily survived in intact animals, prove to be fatal in glucocorticoid deficiency (58). Specifically, in a murine model of adrenal crisis (59), adrenalectomy greatly increased the sensitivity to the lethal effects of TNF α . Adrenalectomised TNF receptor 1a and 1b null mice were resistant to the lethal effects of lipopolysaccharide as were mice treated with anti-TNF serum (59). Thus, considering TNF α as a key mediator of adrenal crisis, glucocorticoid deficiency leads to both enhanced release of TNF α and enhanced sensitivity to TNF α . Furthermore, experimental evidence indicates that TNF α inhibits glucocorticoid receptor functions inducing a state of relative glucocorticoid resistance (60, 61). In summary, lack of suppressive glucocorticoid activity can trigger adrenal crisis via enhanced TNF α secretion, enhanced TNF α sensitivity and TNF α -induced glucocorticoid resistance (Fig. 1).

For other causes of adrenal crisis (e.g. emotional stress and surgery), the underlying mechanisms may be similar, but have been much less studied. For example, surgery may increase the release of TNF α (62) and other cytokines (63) concurrent with the postoperative cortisol increase, and emotional stress may also induce glucocorticoid resistance (64).

Treatment of adrenal crisis

Suspected adrenal crisis requires immediate therapeutic action and, in undiagnosed adrenal insufficiency, treatment usually precedes the biochemical proof of diagnosis.

Table 1 Definition and grading of adrenal crisis (modified from (30)).

Definition:

(A): Major impairment of general health with at least two of the following signs/symptoms

Hypotension (systolic blood pressure <100 mmHg)

Nausea or vomiting

Severe fatigue

Fever

Somnolence

Hyponatraemia (≤ 132 mmol/l) or hyperkalaemia

Hypoglycaemia

(B): Parenteral glucocorticoid (hydrocortisone) administration followed by clinical improvement

Grading:

Grade 1: outpatient care only

Grade 2: hospital care (general ward)

Grade 3: admission to intensive care unit

Grade 4: death from adrenal crisis (with or without parenteral glucocorticoid administration)

Figure 1

Glucocorticoid and cytokine interaction during major infection in patients with intact adrenals (A) and patients with adrenal insufficiency on standard replacement therapy failing to adjust their hydrocortisone doses (B).

Treatment is simple. It consists of parenteral hydrocortisone (initially 100 mg hydrocortisone as a bolus intravenously) and correction of hypovolaemia with isotonic saline (1000 ml isotonic saline within the first hour) (31, 36, 48, 49) (Table 2). Only if hydrocortisone is not available, prednisolone or another synthetic glucocorticoid should be administered in an equivalent dose. Depending on the intercurrent illness, which precipitated the adrenal crisis, additional measures (e.g. antibiotics and thrombosis prophylaxis) are needed (49). This treatment is virtually uniformly successful leading to clinical recovery within 24 h. If improvement does not occur in this time frame, alternative causes for the profoundly impaired health have to be considered again. As has been pointed out in the case vignette, there exists 'a point of no return' where even optimum patient care will no longer avert death from adrenal crisis. Furthermore, in case of long-standing untreated adrenal insufficiency presenting with confusion and somnolence, I have observed that full recovery can take several days or even up to 1 week.

Prevention of adrenal crisis

Physiological endogenous glucocorticoid secretion is highly flexible with rapid adjustments to unexpected needs. When collecting detailed salivary cortisol profiles in healthy students, we were struck by occasional unexplained sharp and high cortisol peaks. Upon questioning, we found out that one was caused by a late-night squash game and another by failing to catch a tram to the University hospital by just a few seconds. In the foreseeable future (if ever), no replacement therapy will be able to fully mimic this amazing adaptive potential of a healthy HPA axis. However, many stressors can be anticipated (e.g. elective surgery) and allow to adjust the glucocorticoid dose to the expected need, thereby preventing the occurrence of clinical deterioration and adrenal crisis. Table 3 gives an overview on treatment adjustments for medical procedures based on recommendations of the UK Addison's disease Self Help Group (49). It is important to understand herein the underlying concept. The recommended dose increase is not intended to mimic the median cortisol increase in healthy subjects during such procedures. Instead, it is intended to mimic the maximum cortisol increase, which may occur in euadrenal subjects triggered during these procedures, potentially induced by some unforeseen events (e.g. postoperative bleeding). Patients with intact adrenal function can respond immediately to such problems with an increase in adrenal cortisol output. By contrast, in adrenal insufficiency, additional glucocorticoids would only be given when clinical deterioration becomes evident. Until then, valuable time may have been lost to adjust the

Table 2 Treatment of adrenal crisis (modified from (49)).

Treatment	Dose/procedure
Hydrocortisone	100 mg bolus given immediately followed by 200 mg/day as continuous infusion or frequent i.v. (or i.m.) boluses (50 mg) every 6 h
Intravenous substitution of fluids	1000 ml of 0.9% sodium chloride during the first 60 min, further fluid administration (0.9% sodium chloride) guided by individual patient needs as assessed clinically or by central venous pressure; frequent haemodynamic monitoring to avoid fluid overload; measurement of serum electrolytes
Depending on the severity of the crisis and on the intercurrent illness	Admission to the intensive care or high-dependency unit; low-dose heparin; antibiotic treatment

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Table 3 Hydrocortisone adjustments for medical procedures (modified from (49)).

Procedure	Preoperative needs	Postoperative needs
Major surgery	Start hydrocortisone infusion (100 mg over 12 h) just before anaesthesia	Continue hydrocortisone infusion (100 mg over 12 h) until able to eat and drink. Then double oral dose for 48+ h, then taper to normal dose
Labour and vaginal birth	Start hydrocortisone infusion (100 mg hydrocortisone over 12 h) at onset of labour	Continue hydrocortisone infusion until delivery (100 mg over 12 h). Double oral dose for 24–48 h after delivery, then taper to normal dose
Minor surgery and major dental surgery	100 mg hydrocortisone before anaesthesia given as a bolus intramuscularly or subcutaneously or as hydrocortisone infusion for the duration of surgery	Double oral dose for 24 h, then return to normal dose
Invasive bowel procedures requiring laxatives	Hospital admission overnight with 100 mg hydrocortisone intramuscularly or subcutaneously and fluid (isotonic saline), repeat dose before start of procedure	Double oral dose for 24 h, then return to normal dose
Dental procedure	Extra morning dose 1 h before surgery	Double oral dose for 24 h, then return to normal dose
Minor procedure	Usually not required	Extra dose (e.g. 20 mg hydrocortisone) if symptoms persist

hydrocortisone dose to the increased need. For that reason, dose adjustments aim at the upper limit of the normal variation to cover such unexpected needs. The short-lived glucocorticoid excess for the majority of patients associated with this strategy apparently carries no significant risks (50, 51, 65).

In emotional or mental stress, I recommend minor dose increases (e.g. 10 mg as an additional dose). For example, in case of a written or oral examination or appearance in court, the additional dose should be taken 1 h before the event. Some patients report a need for a dose increase in strenuous exercise and such a dose increase is mandatory in otherwise sedentary subjects before exhaustive physical exercise (e.g. a mountain tour for several hours in the unprepared). As a rule of thumb, I am rather liberal concerning minor event-related dose increases and more focused on avoiding chronic over-replacement during standard treatment (e.g. 30 mg hydrocortisone or more). Certain drugs enhance (e.g. mitotane, carbamazepine, St Johns wort, and rifampicin) or decrease (grapefruit juice and ritonavir) cortisol metabolism via induction or inhibition of CYP3A4 respectively (66, 67, 68). Here the dose needs to be adjusted accordingly.

As infections are the most frequent cause of adrenal crisis (24, 26, 29, 69), it has been suggested that the patient doubles the hydrocortisone dose if the body temperature increases above 38 °C and triples the dose above 39 °C. This dose is maintained as long as the fever persists and rapidly (within 1–2 days) reduced to the standard replacement dose after recovery. Gastroenteritis poses a

particularly high risk (26, 29), as glucocorticoid availability may be compromised by vomiting and diarrhoea, while the demand is clearly increased. Thus, early parenteral hydrocortisone (100 mg subcutaneously) is strongly recommended either via self-administration or by a physician. This dose may need to be repeated and health-care professionals should be involved early for clinical assessment. Similarly, in severe infection (e.g. pneumonia) with altered cognition, early parenteral hydrocortisone and medical help are warranted (Table 4).

A particularly troubling cause of adrenal crisis is cessation of hydrocortisone therapy by the patient (or by the attending physician!). Careful education of the patient and his relatives is essential. There should be a low threshold for evaluation of a possible psychiatric illness in patients with evidence of poor compliance.

It has been suggested that patients today are at a greater risk of adrenal crisis, because they have less of a ‘cushion’ of excess circulating cortisol with a standard daily dose of 20 mg hydrocortisone compared with the old-fashioned standard dose of 30 mg hydrocortisone (29). However, there is no scientific evidence for such a protective ‘cushion’ effect. Instead, chronic over-replacement may rather increase the susceptibility to infection and thereby increase the risk of adrenal crisis (69).

Patient education

For obvious reasons, patient education is considered essential for crisis prevention, although its efficacy has

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Table 4 Dose adjustments in non-procedural stressful events.

Fever > 38 °C	Double the daily hydrocortisone dose until recovery, then return to standard dose within 1–2 days
Fever > 39 °C	Triple the daily hydrocortisone dose until recovery, then return to standard dose within 2 days
Gastroenteritis with vomiting and/or diarrhoea	Early parenteral hydrocortisone (100 mg subcutaneously or intramuscularly); to be repeated after 6–12 h
Severe infection (e.g. pneumonia/with altered cognition)	Early parenteral hydrocortisone (100 mg subcutaneously or intramuscularly); to be repeated after 6–12 h (49) until recovery
Major emotional or mental stress (e.g. death of a close relative, major university examination)	Addition of 10–20 mg hydrocortisone to the standard replacement dose
Exhaustive strenuous exercise	Add 10 mg hydrocortisone 30–60 min before the exercise

not been well studied. Furthermore, standardised patient education has not yet become a widely available tool in the care of patients with adrenal insufficiency, but has been demonstrated to increase knowledge concerning the disease (70).

As most physicians very rarely encounter an adrenal crisis, they frequently fail to act adequately. There are numerous reports from our patients and others (71) that physicians ignored emergency cards or failed to give parenteral hydrocortisone despite the patient presenting the emergency kit. Thus, I occasionally have given my patients a written text to be signed by any such future emergency physician. It states that the patient has communicated the presence of impending crisis, has shown the emergency card, and the emergency kit. By signature, the physician would thus attest that this evidence was presented, thereby documenting malpractice, if refusing to administer glucocorticoids. I reasoned that asking for the signature would greatly facilitate hydrocortisone administration.

As a consequence of these frequently encountered problems, the essential principle of crisis prevention can be stated as follows:

The well-informed patient (or his/her relative) guides the poorly informed health-care professional!

If so, it becomes mandatory that the patient should indeed be well informed and able to deliver such guidance. However, it has been shown that, despite repeated verbal education, a high percentage of patients (46%) were not sufficiently skilled in coping with physical stress (72). This finding has been confirmed in a more recent investigation including 338 patients with adrenal insufficiency (73). A patient–specialist contact occurring only once a year is, therefore, unlikely to guarantee sufficient education. Thus, the development of improved education concepts remains a major task in future crisis prevention.

Every patient must be provided with an emergency card (31, 48, 49) and I consider the newly designed

European bilingual card a major advantage (74). In addition, every patient should have an emergency set (or two) consisting of 100 mg hydrocortisone for parenteral administration. This injectable hydrocortisone allows immediate action by an attending health-care professional. However, every patient should also be able to self-administer parenteral hydrocortisone and close relatives should also be trained (29, 70). There is ample evidence that provision with injectable hydrocortisone is incomplete (29, 30) and that many patients provided with hydrocortisone for self-administration fail to use it, when needed (29, 75). Thus, in our unit, training for self-administration of hydrocortisone has been prioritised in patient education. Importantly, we have recently demonstrated that s.c. hydrocortisone is rapidly absorbed with only a short delay compared with i.m. injection (76). Patients clearly prefer s.c. over i.m. injection, as would I. Reducing barriers to self-injection are most important in my view and the ease of s.c. injection far outweighs the short delay (11 min) in reaching concentrations above 1000 nmol/l (22 min compared with 11 min after i.m. injection) (76). This small time difference compares very favourably with current time lines from contacting health professionals until their eventual hydrocortisone injection in impending crisis (43). In fact, in my view, a clearly bigger problem is related to the current emergency sets, which often are not simple enough for rapid and easy handling by an already compromised patient. Accordingly, some patients have reported that the speed of development of their crisis had taken them by surprise, so that they were too weak to prepare the injection by the time they realised that they needed it (29). Thus, only the availability of a hydrocortisone pen will fully remove current delays in timely parenteral hydrocortisone self-administration. As industry is reluctant to develop such a device, public funding is needed. This approach has been apparently successful in the case of adrenaline autoinjectors for anaphylaxis.

In conclusion, reduction of morbidity and elimination of mortality from adrenal crisis should become a top priority for adrenal endocrinologists aiming at a 50% reduction in crisis-related deaths within the following 10 years. To this end, it will be helpful to better understand the physiopathology of adrenal crisis to define optimum dose adjustments. Furthermore, patient education must move forward to a structured and quality-controlled approach offered to every single patient. Hydrocortisone self-administration is a critical part of patient education and would be greatly facilitated by the availability of a hydrocortisone pen. Public funding may be needed to make such a pen become a reality. Implementing these key measures will undoubtedly help to achieve a substantial reduction in mortality from adrenal crisis.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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