Original Article

Stress Doses of Glucocorticoids Cannot Prevent Progression of All Adrenal Crises

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Abstract. Adrenal crises (ACs) sometimes progress rapidly and can be fatal. The aims of the present study were to reveal whether stress doses of glucocorticoids (SDGs) can prevent progression of severe ACs and to suggest a method of prevention, through analysis of its clinical features. We studied 24 severe ACs (nine patients) that occurred after diagnosis of primary or secondary adrenal insufficiency, retrospectively. The following information was analyzed: 1) whether SDGs were given orally and/or sc; 2) duration from the time when some symptoms started to the time when the patient came to the hospital; and 3) presence of hypoglycemia and electrolyte disturbance (hyponatremia, hyperkalemia). Eleven crises occurred after taking SDGs. Ten crises progressed within 3 h. Six of these ten crises progressed to severe ACs despite the fact that the patients took SDGs. Six crises were observed in association with hypoglycemia, and five of these six crises occurred in patients under 5 yr of age. Three of the six crises in association with hypoglycemia progressed to ACs within 3 h. Two of the three crises progressed to severe status within 3 h despite the fact that the patients took SDGs. Electrolyte disturbance was observed in only one crisis. In conclusion, SDGs cannot prevent progression of all ACs. Progression can be associated with hypoglycemia, particularly in patients under 5 yr of age. Patients should be given guidance on an ongoing basis on how to prevent ACs and hypoglycemia.

Key words: adrenal crisis, stress doses of glucocorticoids, hypoglycemia, electrolyte disturbance, young children

Introduction

In patients with primary or secondary adrenal insufficiency, adrenal crises (ACs) may develop when they are subjected to stress, such as infection. Therefore, these patients require stress doses of glucocorticoids (SDGs).

As ACs can be fatal (1–3), it is pivotal that they be prevented and managed at home. Understanding the clinical features of severe ACs is helpful in their prevention. However, a search of Pubmed revealed no studies available in regard to clinical features in which a large number of cases of severe ACs were analyzed. In addition, there were also no studies that investigated the usefulness of SDGs, except for case reports asserting that SDGs failed to prevent
hypoglycemia (4, 5).

Therefore, the aims of the present study were 1) to reveal whether SDGs can prevent progression of severe ACs and 2) to suggest a method of prevention, through analysis of their clinical features.

Subjects

This retrospective study was conducted using patients experiencing severe ACs after diagnosis of adrenal insufficiency (explained below).

The original cohort was eleven patients with primary or secondary adrenal insufficiency who were treated due to ACs at our hospital from January 1985 to June 2005. The total number of ACs was 49. Glucocorticoid replacement therapy using hydrocortisone (cortisol) was used for all patients. Mineralocorticoid replacement was also prescribed to patients with primary adrenal insufficiency. The daily doses of hydrocortisone were 13.1–18.8 and 1.6–15 mg/m²/day in primary and secondary adrenal insufficiency, respectively.

The inclusion criteria of the present study were as follows; 1) patients and their parents were already instructed on how to take SDG (hydrocortisone orally at 80–100 mg/m²/day divided into four doses per day, and a 20–25 mg/dose sc injection); 2) the crises occurred outside of the hospital; and 3) the symptoms satisfied the following definition of severe AC on arrival, so that patients who needed treatment for severe ACs could be selected. They must have experienced at least one of the following symptoms, unconsciousness, convulsion or hypotension (blood pressure was under 60 mmHg or pulse could not be palpated), or at least one symptoms indicating circulatory failure (pale facial color, weak pulsation or cold extremities) with definitive causes of adrenal crises (traffic accident, infection with CRP above 10 mg/dl or torsion of an ovarian cyst).

Consequently, 24 crises in nine patients were evaluated in the present study (Table 1). The median age at crisis was 4 yr and 0 mo of age (7 mo to 24 yr of age). As severe ACs in association with hypoglycemia were examined in the present study, patients with hypopituitarism who did not start GH therapy were excluded.

Methods

The following information were analyzed: 1) whether SDGs were given orally and/or sc before arrival to the hospital; 2) ‘duration before arrival’, which was the duration from the time some symptoms started that could be related to AC (for example, vomiting or fever) to the time when the patient came to hospital; and 3) presence of hypoglycemia and electrolyte disturbance (hyponatremia and hyperkalemia).

In the present study, a serum glucose concentration of less than 40 mg/dl was defined as hypoglycemia, a serum Na concentration of less than 130 mEq/L was defined as hyponatremia and a serum K concentration of over 5.5 mEq/L was defined as hyperkalemia.

Results

SDGs at home

Eleven severe ACs (four patients; 7 mo to 21 yr of age) occurred even though SDGs were given at home (orally and/or sc; Table 1). Among these eleven crises, SDGs were given orally in seven crises and were given sc in six crises. Another eleven crises occurred in patients (seven patients; 1 to 24 yr of age) who came to the hospital without administration of glucocorticoid. In at least two of the latter eleven crises, the ACs progressed so rapidly that the patients had no time to take SDGs. No information was available for the remaining two crises.

Duration before arrival

Ten (five patients; 8 mo to 24 yr of age) of the 24 crises progressed rapidly within 3 h (Table 1). Six (four patients; 8 mo to 21 yr of age) of
these ten crises progressed to severe ACs within 3 h, even though SDGs were administered (Table 2). Duration before arrival was from 3 to 24 h in seven ACs (five patients) and was from 24 to 72 h in another seven crises (six patients; Table 1).

### Hypoglycemia and electrolyte disturbances

**Hypoglycemia:** Six crises (three patients) in association with hypoglycemia (<5–35 mg/dl) were observed in the morning after overnight fast (Table 1). Unconsciousness was observed in one crisis, and convulsions were observed in the other five. Five of these six crises were observed in patients with secondary adrenal insufficiency, and the other one was observed in a patient with primary adrenal insufficiency.

In the above six crises with hypoglycemia, five crises (three patients) occurred in patients under 5 yr of age (1 to 4 yr of age; 13 of the 24 crises occurred in patients under 5 yr of age). The remaining crisis occurred in an 8-yr-old maltreated boy with hypopituitarism (Patient 7 in Table 1). This patient died due to this crisis.
He had severe mental retardation due to frequent episodes of hypoglycemia.

Hypoglycemia was observed in three crises (one patient) even though the patient came to the hospital after sc injections of SDGs (Table 2). Duration before arrival was within 3 h in three of the six crises with hypoglycemia (Table 1). Two of the three crises progressed to severe status within 3 h despite SDGs (Table 2).

Electrolyte disturbance: In secondary adrenal insufficiency, no abnormalities in the serum Na or K concentrations were observed. Even in primary adrenal insufficiency, ACs progressed to severe states without electrolyte disturbance, with the exception of one crisis. This crisis occurred in an 11-mo-old girl with CYP21A2 deficiency (Na 118 mEq/L, K 5.8 mEq/L) despite SDGs (Patient 1 in Table 1).

**Discussion**

SDGs could not prevent progression of all severe ACs. Rapid progression and infantile hypoglycemia (under 5 yr of age) were observed despite SDGs. One possible reason why the SDGs could not prevent progression of all ACs is that the dose of glucocorticoids may be insufficient. This should be studied in the near future.

In regard to prevention of severe ACs, it is important 1) to take SDGs (the earlier, the better), 2) to come to the hospital if no improvement is seen after taking SDGs, and 3) to control hypoglycemia in young children. To make these possible, we first need to instruct patients and/or their patients on when to take SDGs (orally and sc) on an ongoing basis. To enable sc administration as early as possible, we should ensure that the patients most likely to have severe ACs, such as young children less than 5 yr of age, or their parents have a syringe of hydrocortisone. Furthermore, the patients should come to the hospital quickly, if they do not improve after taking SDGs. Finally, control of hypoglycemia is necessary to prevent severe ACs in young children less than 5 yr of age. There have been several reports of children with primary or secondary adrenal insufficiency presenting severe ACs with hypoglycemia (4–12), and some of these crises resulted in death (6, 10–12). We recommend measurement of the patient’s glucose level at home, especially in the morning (12), in the same manner as is now widely performed in patients with type1 diabetes mellitus. In patients under stress, it is advisable to supply them with sugar-rich foods or drinks with SDGs, especially young children. This importance of prevention of hypoglycemia in AC has previously been indicated in case reports concerning congenital adrenal hyperplasia in the 1970s and 1980s (4, 5).

**Table 2** Stress doses of glucocorticoids (SDGs)

|                                | SDGs (+) | SDGs (-) | Total |
|--------------------------------|----------|----------|-------|
| Duration before arrival < 3 h  | 6        | 4        | 10    |
| Hypoglycemia                   | 3        | 3        | 6     |
| Hypoglycemia + duration before arrival < 3 h | 2  | 1        | 3     |

#1 Ten crises progressed rapidly within 3 h. Six out of these ten crises progressed within 3 h despite SDGs. #2 Six crises with hypoglycemia were observed. Hypoglycemia was observed in three patients despite SDGs. #3 Duration before arrival was within 3 h in three of the six crises with hypoglycemia. Two of the three crises progressed to severe status within 3 h despite SDGs.
progression of all ACs. Progression can be associated with hypoglycemia, particularly in patients under 5 yr of age. Patients should be given guidance on an ongoing basis on how to prevent ACs and hypoglycemia.

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