Rectal hydrocortisone during stress in patients with adrenal insufficiency

M De Vroede, R Beukering, M Spit and M Jansen

Arch. Dis. Child. 1998;78;544-547

Rectal hydrocortisone during stress in patients with adrenal insufficiency

M De Vroede, R Beukering, M Spit, M Jansen

Abstract

***Objective*—Patients with glucocorticoid deficiency need lifelong glucocorticoid replacement treatment. During acute stressful events, steroid dosage must be increased several times, which is often problematical in children. This study investigated the reliability of rectal hydrocortisone administration as an alternative to the intramuscular route.**

***Study design*—Serum cortisol was assessed during stress in normal children to determine the concentration that should be achieved after rectal hydrocortisone. Subsequently, serum cortisol concentrations were measured three hours after administering a suppository containing hydrocortisone 100 mg/m^2 to 57 patients with adrenocortical insufficiency. In eight patients, the time dependency of the cortisol rise after rectal administration was established.**

***Results*—In 51 previously healthy children admitted to hospital with an acute stressful condition, the mean serum cortisol concentration was 1092 nmol/l. Rectal hydrocortisone in patients with adrenocortical insufficiency resulted in a mean serum cortisol concentration of 1212 nmol/l three hours after insertion of the suppository containing hydrocortisone. In 14 of 57 children, serum cortisol was < 1000 nmol/l and in eight children it was below 600 nmol/l. One hour after administration, the mean cortisol concentration had reached 1000 nmol/l. This was sustained for more than four hours.**

***Conclusion*—Rectal hydrocortisone is a safe alternative to parenteral administration in the self management of Addisonian prone conditions. However, because eight of 57 children did not achieve concentrations > 600 nmol/l, its use is recommended only after previously documenting an adequate serum cortisol concentration three hours after receiving a test dose.**

(*Arch Dis Child* 1998;**78**:544–547)

Keywords: adrenal insufficiency; hydrocortisone; suppository

Department of Pediatrics, Wilhelmina Children's Hospital, Utrecht University, PO Box 18009, 3501 CA Utrecht, Netherlands
M De Vroede
R Beukering
M Spit
M Jansen

Correspondence to:
Dr De Vroede.
email: M.DeVroede@WKZ.AZU.NL

Accepted 14 January 1998

Patients suffering from adrenocortical insufficiency need lifelong steroid treatment. When stressed, their glucocorticoid dose must be increased threefold to fivefold. Children may be unwilling to ingest the increased dose or unable to do so because of vomiting. Parenteral steroid administration is then indicated. Unless parents are able to administer the injection themselves, there may be a potentially dangerous delay. Therefore, we sought an alternative route to administer high doses of steroids during those situations that preclude oral intake. Newrick and colleagues[1] reported in adults that rectal hydrocortisone can be used as an alternative to intramuscular hydrocortisone. Serum cortisol concentrations comparable with those found in stressed adults were achieved following rectal hydrocortisone at a dose of 200 mg. Because the use of rectal hydrocortisone in young patients has not been reported we set up the present study to examine the efficacy of rectal hydrocortisone administration during stressful situations in children.

We considered the following questions. What serum cortisol concentrations are reached under various stressful circumstances in previously healthy children? Is it possible to obtain such values using rectal hydrocortisone? If so, what is the time course for serum cortisol concentrations after rectal administration?

Subjects and methods

SERUM CORTISOL CONCENTRATIONS DURING STRESS

Fifty one children (15 girls, 36 boys), aged 1 month to 17 years participated in the study. All had been healthy until admission. Previous or current steroid users were excluded. Twenty six patients had presented in the outpatient clinic, predominantly with fever (rectal temperature > 38°C), seizures, and respiratory or urinary infections (table 1). Twenty five patients were admitted to the intensive care unit because of life threatening events. The group of children admitted to the intensive care unit had the same age distribution as those in the outpatient clinic (table 1). Capillary blood for cortisol determination was drawn during diagnostic

Table 1 Clinical characteristics and mean serum cortisol in 51 children with various degrees of stress

Diagnosis	*n*	*M*	*F*	*Age (years) Mean (SEM)*	*CRP (ng/ml) Mean (range)*	*Cortisol (nmol/l) Mean (SEM)*
Outpatients	26	17	9	2.9 (0.6)	33.8 (3–262)	1029 (80)
Upper airway infection	14	10	4	1.5 (0.3)	19.6 (3–71)	972 (112)
Pneumonia	8	5	3	4.7 (1.8)	60.1 (5–262)	1279 (127)
Others*	4	2	2	4.3 (0.5)	31.3 (3–109)	730 (70)
Intensive care patients	25	19	6	2.7 (0.6)	51.0 (0–294)	1156 (110)
Severe infectious disease†	6	4	2	4.1 (2.0)	117.6 (16–294)	1127 (197)
Respiratory failure	5	3	2	1.2 (0.7)	12 (0–27)	950 (245)
Laryngitis/epiglottitis	5	4	1	3.0 (1.0)	32.6 (4–120)	1214 (233)
Status epilepticus	4	3	1	2.3 (0.7)	5.7(0–14)	1488 (121)
Others‡	5	5	0	2.3 (1.9)	64.8 (4–221)	1076 (379)
All patients	51	36	15	2.8 (0.5)	42.2 (0–294)	1092 (67)

*Patients presenting with either seizures, urinary tract infection, cellulitis or cyanotic spell.
†Including sepsis, endocarditis, abdominal abscess.
‡Patients presenting with viral diseases, haemolytic uraemic syndrome, epidermolysis bullosa or metabolic coma.
CRP, C reactive protein; F, female, M, male.

Table 2 Serum cortisol concentrations three hours after rectal hydrocortisone administration (100 mg/m²) in 57 children with adrenocortical insufficiency

Diagnosis	*n*	*M*	*F*	*Age (years) Mean (SEM)*	*Cortisol (nmol/l) Mean (SEM)*
Primary insufficiency	27	14	13	6.2 (0.9)	1192 (95)
Congenital adrenal hyperplasia	24	11	13	6.1 (0.9)	1158 (96)
Congenital adrenal hypoplasia	3	3	0	(0.6, 4, 17)*	1460
Secondary insufficiency	28	15	13	8.6 (0.9)	1207 (101)
Astrocytoma	3	2	1	(7, 12, 17)*	1230
Craniopharyngioma	5	2	3	10.0 (0.9)	880 (270)
Non-tumorous panhypopituitarism	17	9	8	8.0 (1.3)	1220 (110)
Isolated ACTH deficiency	3	2	1	(1, 7, 11)*	1673
Miscellaneous†	2	1	1	(16, 16)*	1250
All patients	57	30	27	7.7 (0.7)	1212 (70)

*Age of each patient (years).
†One patient with adrenal insufficiency after pituitary surgery for Cushing's disease; one patient with idiopathic thrombocytopenic purpura and prednisone induced adrenal insufficiency.
F, female; M, male.

procedures in the outpatient clinic or on arrival at the intensive care unit.

SERUM CORTISOL CONCENTRATIONS FOLLOWING RECTAL HYDROCORTISONE ADMINISTRATION IN PATIENTS WITH ADRENOCORTICAL INSUFFICIENCY

Fifty seven children with adrenal insufficiency (27 girls, 30 boys), aged 1 month to 17 years, were included in the study (table 2). All of them had adequate replacement treatment with thrice daily hydrocortisone administration. Twenty seven patients had primary adrenal insufficiency, mainly as a result of congenital adrenal hyperplasia. Among the 28 patients with secondary adrenal insufficiency, 17 had neonatal or idiopathic panhypopituitarism, eight developed panhypopituitarism after surgery for craniopharyngioma (five) or astrocytoma (three), and three had isolated adrenocorticotrophic hormone (ACTH) deficiency. All patients were biochemically well controlled at the time of the study. They were prescribed hydrocortisone suppositories, 100 mg/m² in Witepsol W45 base and asked to insert one suppository three hours before the endocrine clinic visit. The dose ordinarily scheduled at that time was omitted. Capillary blood for cortisol determination was drawn during the visit.

TIME COURSE OF SERUM CORTISOL AFTER RECTAL ADMINISTRATION

In eight patients, serial samples were taken for cortisol determination after rectal hydrocortisone (100 mg/m²) administration, given at eight o'clock in the morning instead of the normal oral hydrocortisone dose taken at that time. Five were inpatients who had blood drawn via an indwelling catheter before and at one, two, four, and eight hours after rectal hydrocortisone administration. Three patients with congenital adrenal hyperplasia performed the study at home by collecting samples through fingertip punctures. Samples were sent to the hospital and prepared for assay on arrival. The feasibility of this procedure, as well as the stability of the serum cortisol concentration in the sample in terms of storage temperature and delay between the puncture and the actual measurement, was validated in three volunteers before the study.

LABORATORY DETERMINATIONS

Plasma samples of cortisol were assayed by a fluorescence polarisation immunoassay developed by Abbott (Abbott Laboratories, Illinois, USA); the intra-assay and interassay coefficients of variation are reported to be less than 10%.[2] The detection limit is 10 nmol/l. The cross reactivity in the cortisol assay of 17-hydroxyprogesterone and 11-deoxycortisol are 0.5% and 4.7%, respectively (manufacturer's data).

MEDICATION AND CONSENT

The suppositories (100 mg/m² hydrocortisone in a Witepsol W45 base) were prepared by the patients' local pharmacists. For time course studies carried out in the hospital, the suppositories were provided by the hospital pharmacy. Permission for the study was given by the local ethics committee. Informed consent was obtained from all patients and/or their parents.

Results

SERUM CORTISOL CONCENTRATIONS IN PREVIOUSLY HEALTHY CHILDREN

In the group of 51 previously healthy children, mean serum cortisol was 1092 nmol/l. Although the nature of the acute stress was more severe in the intensive care unit group, serum cortisol was only slightly higher in the intensive care unit group than in the outpatient clinic group: 1156 (110) nmol/l *v* 1029 (80) nmol/l (mean (SEM)). The data from two patients in the intensive care unit group were omitted from analysis because of excessively high cortisol values (3030 and 3100 nmol/l, one of which was obtained postmortem).

SERUM CORTISOL CONCENTRATIONS AFTER RECTAL HYDROCORTISONE ADMINISTRATION IN PATIENTS WITH ADRENOCORTICAL INSUFFICIENCY

In the patient group, mean serum cortisol three hours after rectal administration of 100 mg/m² hydrocortisone was 1212 nmol/l (table 2). Forty three of 57 patients had a serum cortisol concentration > 1000 nmol/l, 11 of whom had concentrations of 1500 nmol/l or even higher. Eight of 57 patients had a value < 600 nmol/l; two of these patients were younger than 6 months when tested. Mean serum cortisol concentrations in patients with primary or secondary insufficiency were similar. In those with secondary adrenocortical deficiency related to an intracranial tumour, however, differences appeared when results were analysed according to aetiology. While the three patients who had surgery or radiation for astrocytoma reached a serum cortisol concentration of ~ 1000 nmol/l, three of five patients with a craniopharyngioma had values < 600 nmol/l (320, 440, and 580 nmol/l, respectively). All three were overweight.

In most patients we obtained a single measurement. In three patients, rectal hydrocortisone administration and subsequent serum cortisol measurements were repeated three times and resulted in similar values, suggesting that the values obtained were reproducible.

TIME COURSE

After inserting the suppository, serum cortisol in seven patients increased from almost undetectable baseline values to 960 nmol/l at one

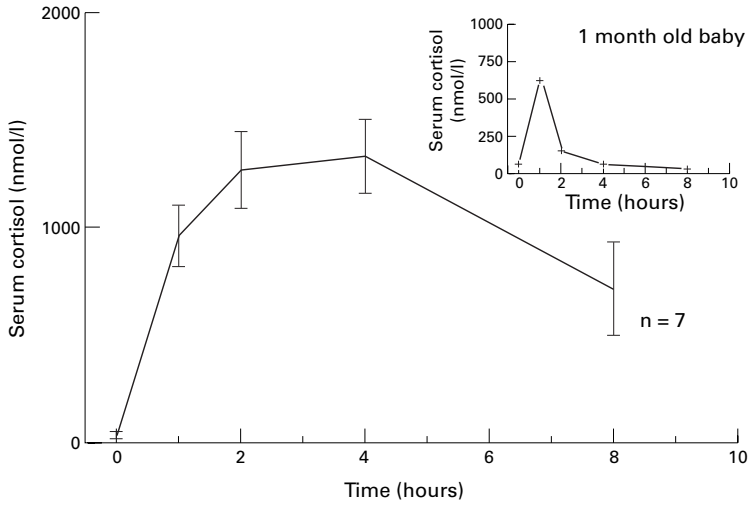

Figure 1 Eight patients with adrenocortical insufficiency were asked to insert a 100 mg/m² suppository at 08:00. Blood for cortisol measurement was drawn before administration and at the indicated time points. Results of seven patients are expressed as the mean (SEM). The insert represents the time course in a 1 month old baby who extruded the suppository a few minutes after administration.

hour, after which it remained at > 1000 nmol/l for about four hours (fig 1). Eight hours after inserting the suppository, the mean serum cortisol was 720 nmol/l. The eighth patient, a 4 week old baby, extruded the suppository within minutes after insertion. Despite this, we observed a cortisol peak of 620 nmol/l at one hour, after which the cortisol concentration declined rapidly (fig 1).

Discussion

Even when adequately substituted with hydrocortisone, patients with adrenocortical insufficiency are in danger of adrenocortical crises during intercurrent illness if they are unable to ingest supplementary glucocorticoids. Children pose special problems in this respect—they vomit easily or may refuse to take the medication, leaving parenteral administration as the only way to achieve adequate steroid concentrations. Frequently, there is substantial delay before the glucocorticoid preparation is injected, resulting in an imminent or overt adrenal crisis and hospitalisation, which might have been avoided. Based on the experience of Newrick in adult patients,[1] we tested rectal hydrocortisone and found it to be a valuable alternative to increased doses of oral glucocorticoids in stressful situations.

We chose a preparation containing hydrocortisone in a Witepsol W45 base. This is a hydrophobic base composed mainly of triglycerides, the lipophilic character of which enhances rectal absorption. The hydrocortisone dose of 100 mg/m² administered to the children was based on the dose of 200 mg that Newrick gave to adults (with a normative body surface area of 1.73 m²). Because our goal was for children to use these suppositories at home, we deliberately decided to ask their own pharmacist to prepare this relatively simple prescription. The consistency of our results did not prompt us to assay the suppositories for their steroid content.

The mean serum cortisol measured in an unselected group of children with normal adrenal function who presented with various illnesses was about 1000 nmol/l, which is similar to the values reported by Newrick *et al* in adult stressed patients.[1] Using this value as a cut off point with respect to adequacy of steroid concentrations during stress, 43 of our 57 patients with adrenocortical insufficiency were adequately covered by the hydrocortisone suppository. The question then arises whether the rectal route failed in the remaining 14 patients or whether our proposed cut off point of 1000 nmol/l is too high. The latter might be the case—in a study of 76 febrile children, Nickels and Moore[3] found serum cortisol values of 820 (40) nmol/l (mean (SEM)). Other reports mention similar values during surgical procedures in children,[4 5] with the exception of a study by Rosendahl and colleagues,[6] who found concentrations of 1150 (150) nmol/l (mean (SEM)) in 20 children during surgery. Interestingly, the cortisol response to 0.25 mg ACTH in children over the age of 1 year is in the range of 600–800 nmol/l.[7] Therefore, it could be argued that a serum cortisol value between 600 and 1000 nmol/l provides adequate steroid coverage during stress in children. However, this statement does not apply to patients whose serum cortisol values did not rise above 600 nmol/l, which was the case in eight of our children. We have several possible explanations for this failure. The quick extrusion of the suppository with a bowel movement is a potential problem, especially in very young children and was seen in at least one of the eight patients. In some patients, diarrhoea might have interfered with drug absorption. Low concentrations of corticosteroid binding globulin (CBG) could also be responsible for lower serum cortisol values; unfortunately, we did not measure CBG values systematically. Obesity is associated with increased cortisol production and increased excretion of cortisol metabolites[8]; this might explain the low values found in three patients with secondary adrenal insufficiency and hypothalamic obesity. Finally, because we did not measure the hydrocortisone concentration in the suppositories, we cannot completely rule out errors that might have occurred during their preparation.

The time course of the cortisol concentrations following rectal administration shows that adequate concentrations are almost invariably reached after an hour and persist for at least six hours. Therefore, we instruct parents to insert a suppository whenever oral administration is impossible and repeat it every eight hours until the child is able to ingest steroids by mouth. This strategy has worked well in ~ 20 of our patients so far—all parents reported improvement of fatigue and cessation of vomiting within about an hour, which can be expected in view of the time course. Likewise, it is conceivable that the rapid increase in serum cortisol observed in the 1 month old baby, who extruded the suppository after a few minutes, would allow such a child to deal temporarily with stress and might enable resumption of oral intake.

Following availability of these suppositories in 1993, hospital admissions for incipient

adrenal crisis in our patients were reduced to only one patient, in whom severe diarrhoea precluded the rectal route.

We conclude that rectal hydrocortisone administration is a safe alternative in the treatment of stress conditions whenever oral replacement is not feasible. It seems wise, however, to check the serum cortisol concentration three hours after rectal hydrocortisone administration of a test dose of 100 mg/m^2, especially in very young or obese patients. If the concentration is > 1000 nmol/l, we advise administering suppositories whenever the oral route precludes adequate intake. Values < 1000 nmol/l warrant further investigations such as a re-check of the cortisol concentration, the use of a suppository prepared by the hospital pharmacist, or a dose increase to 150–200 mg/m^2. Although concentrations of 600–1000 nmol/l might be sufficient for stress coverage, we prefer a serum cortisol value of 1000 nmol/l as a prerequisite for suppository use and strongly discourage the rectal route of steroid administration during stress for those children in whom the concentration is below 600 nmol/l. Parents of very young children should be made aware of the danger of premature extrusion of the suppository. In any case, if the child's condition does not improve within one hour, parenteral steroids should still be given.

We thank Dr CMA Rademaker, hospital pharmacist, for practical advice.

Part of this study was presented at the 35th annual meeting of the European Society for Paediatric Endocrinology, Montpellier (France), September 1996.

1 Newrick PG, Braatvedt G, Hancock J, Corrall RJM. Self-management of adrenal insufficiency by rectal hydrocortisone. *Lancet* 1990;i:212–13.
2 Jonetz-Mentzel L, Wiedemann G. Establishment of reference ranges for cortisol in neonates, infants, children and adolescents. *Eur J Clin Chem Clin Biochem* 1993;**31**:525–9.
3 Nickels DA, Moore DC. Serum cortisol responses in febrile children. *Pediatr Infect Dis J* 1989;**8**:16–19.
4 Khilnani P, Munoz R, Salem M, Gelb C, Todres ID, Chernow B. Hormonal responses to surgical stress in children. *J Pediatr Surg* 1993;**28**:1–4.
5 Wolf AR, Eyres RL, Laussen PC, *et al.* Effect of extradural analgesia on stress responses to abdominal surgery in infants. *Br J Anaesth* 1993;**70**:654–60.
6 Rosendahl W, Schulz U, Teufel T, Irtel von Brenndorf C, Gupta D. Surgical stress and neuroendocrine responses in infants and children. *J Pediatr Endocrinol Metab* 1995;**8**:187–94.
7 Lashansky G, Saenger P, Fishman K, *et al.* Normative data for adrenal steroidogenesis in a healthy pediatric population: age- and sex-related changes after adrenocorticotropin stimulation. *J Clin Endocrinol Metab* 1991;**73**:674–86.
8 Orth DN, Kovacs WJ, Debold CR. The adrenal cortex. In: Wilson JD, Foster, DW, eds. *Williams textbook of endocrinology.* Philadelphia: WB Saunders, 1992:512.