Early report

Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment

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Summary

Background Suppression of the adrenal response is an unpredictable consequence of glucocorticoid treatment. To investigate the kinetics of the adrenal response after short-term, high-dose glucocorticoid treatment, we measured the adrenal response to the low-dose (1 μg) corticotropin stimulation test.

Methods We studied 75 patients who received the equivalent of at least 25 mg prednisone daily for between 5 days and 30 days. After discontinuation of glucocorticoid treatment, 1 μg corticotropin was administered intravenously, and stimulated plasma cortisol concentrations were measured 30 min later. In patients with a suppressed response to 1 μg corticotropin, the test was repeated until stimulated plasma cortisol concentrations reached the normal range.

Findings The adrenal response to 1 μg corticotropin was suppressed in 34 patients and normal in 41. Subsequent low-dose corticotropin tests showed a steady recovery of the adrenal response within 14 days. In two patients, the adrenal response remained suppressed for several months. There was no correlation between plasma cortisol concentrations and the duration or dose of glucocorticoid treatment.

Interpretation Suppression of the adrenal response is common after short-term, high-dose glucocorticoid treatment. The low-dose corticotropin test is a sensitive and simple test to assess the adrenal response after such treatment.

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Introduction

Short-term, high-dose treatment with synthetic glucocorticoids is used in a range of inflammatory and immunological disorders. Among the many biochemical and metabolic effects of glucocorticoid treatment, the suppression of the adrenal response is a major and unpredictable complication.[1,2] Neither the dose and duration of glucocorticoid treatment nor a random plasma cortisol measurement are reliable indicators of probable adrenal insufficiency.[3–5] Therefore, stimulation tests are used to assess the adrenal response.[6,7] The low-dose (1 μg) corticotropin test[8] is sensitive in revealing partial adrenal insufficiency,[9,10] by providing physiological adrenocortical stimulation.[11] The results of the low-dose corticotropin test correlate closely with those of the insulin-induced hypoglycaemia test,[12] the generally agreed reference standard,[13,14] and are superior to those of the standard (250 μg) short corticotropin test.[10,15]

We aimed to find out the frequency of a suppressed adrenal response by means of the low-dose (1 μg) corticotropin test in patients who had received short-term, high-dose glucocorticoid treatment. We also aimed to ascertain the time to full recovery of the normal adrenal response in patients with a deficiency of the response.

Methods

Participants

Between July, 1997, and June, 1998, we undertook a prospective cohort study in a large urban hospital, including patients who were receiving glucocorticoid treatment for the first time in their lives. Reasons for therapy were varied: chronic obstructive lung disease, cancer chemotherapy, neurological disorders, inflammatory bowel disease, collagen vascular disorders, anaphylaxis, and thyrotoxicosis. We excluded patients with a history of previous glucocorticoid treatment, Addison's disease, adrenal metastases, Cushing's disease, pituitary adenoma, or acute myocardial infarction. The low-dose (1 μg) corticotropin test was done in 75 patients (35 women and 40 men; median age 65 years [range 18–87]). Short-term was defined as a treatment duration of between 5 days and 30 days.

The drugs used were prednisone, prednisolone, methylprednisolone, and dexamethasone. The doses are given here as prednisone equivalent doses (1·0 mg methylprednisolone and 1·0 mg dexamethasone equivalent to 1·2 mg and 7·5 mg prednisone, respectively). High-dose was defined as a daily dose of at least 25 mg prednisone equivalent. The study was approved by the institutional review committee, and informed consent was obtained from all participants.

Procedures

For the low-dose corticotropin test, a bolus intravenous injection of 1 μg (1–24)-corticotropin (tetracosactrin, Synacthen, Novartis Pharma, Berne, Switzerland) was given. One vial of 250 μg tetracosactrin was diluted in sterile saline solution to a concentration of 1 μg/mL, filtered in plastic syringes, and stored at

	Normal adrenal response (n=41)	Suppressed adrenal response (n=34)	p
Demography			
Age (years)*	66 (23–87)	63·5 (18–85)	0·54
M/F	21/20	19/15	· ·
Diagnosis			
Chronic obstructive lung disease/asthma	10	7	· ·
Cerebral oedema	8	5	· ·
Cancer	8	10	· ·
Inflammatory bowel disease	4	1	· ·
Vasculitis	1	3	· ·
Thyrotoxicosis	3	· ·	· ·
Autoimmune haemolytic anaemia	2	2	· ·
Anaphylaxis	3	2	· ·
Spinal stenosis/paraparesis	· ·	4	· ·
Guillain-Barré syndrome	1	· ·	· ·
Bell's palsy	1	· ·	· ·
Body-mass index (kg/m²)†	23·4 (3·8)	24·9 (5·3)	0·24
Laboratory measurements			
Systolic blood pressure (mm Hg)*	130 (100–180)	120 (100–160)	0·06
Potassium (mmol/L)†	4·0 (0·3)	3·9 (0·4)	0·72
Glucose (mmol/L)*	6·8 (4·4–25·9)	5·9 (4·3–17·6)	0·04
White-cell count (×10³/L)*	8·9 (0·6–22·8)	8·9 (4·2–21·4)	0·38

*Median (range); difference tested by Mann-Whitney test.
†Mean (SD); difference tested by Student's *t* test.

Baseline characteristics of participating patients

4°C.[8] The tests were carried out between 24 h and 72 h after the discontinuation of the glucocorticoid treatment, at 0800 h after an overnight fast. Blood samples were taken for measurement of basal plasma cortisol concentration, glucose, and electrolytes, and white-cell count. 1 μg corticotropin was administered intravenously via cannula (Vasofix, Braunüle, B Braun, Melsungen, Germany) and a further blood sample was taken after 30 min for measurement of stimulated plasma cortisol concentration.

A normal response to intravenous corticotropin was defined as a stimulated plasma cortisol concentration above 550 nmol/L. This cut-off value was chosen to increase sensitivity[8,16–18] and to allow comparison with the response to the standard (250 μg) short corticotropin test in this laboratory.

In patients with a deficient adrenal response to 1 μg corticotropin, additional low-dose corticotropin tests were done on days 2, 4, 6, 10, 12, and 14, until stimulated plasma cortisol concentrations reached the normal range. In patients with a suppressed adrenal response on day 14, further low-dose corticotropin tests were done after 3 months and 6 months.

Plasma cortisol was measured by fluorometric EIA (Dade Stratus, AHS, Merz and Dade, Munich, Germany). The within-assay and between-assay coefficients of variation were 5·1% and 4·1%. The sensitivity of the assay was 7·2 nmol/L. The assay was highly specific for cortisol, with low cross-reactivity to other glucocorticoids. (To convert values for plasma cortisol concentrations from nmol/L to μg/dL, multiply by 0·036.)

Blood glucose concentrations were measured by the hexokinase method (Gluco-quant, Boehringer Mannheim, Germany), and serum potassium concentrations were measured by direct potentiometry.

Analysis

All statistical analyses used SigmaStat, Statistical Analysis System, version 1.0. If data were normally distributed (checked by Kolmogorov-Smirnov test), Student's *t* test was used to compare groups. Otherwise the Mann-Whitney rank-sum test was used. Relations between variables were analysed by linear regression analysis.

Results

41 (55%) of the 75 study patients had stimulated plasma cortisol concentrations above 550 nmol/L and were classified as having a normal adrenal response; the other 34 patients (45%) had stimulated plasma cortisol concentrations below this cut-off (table).

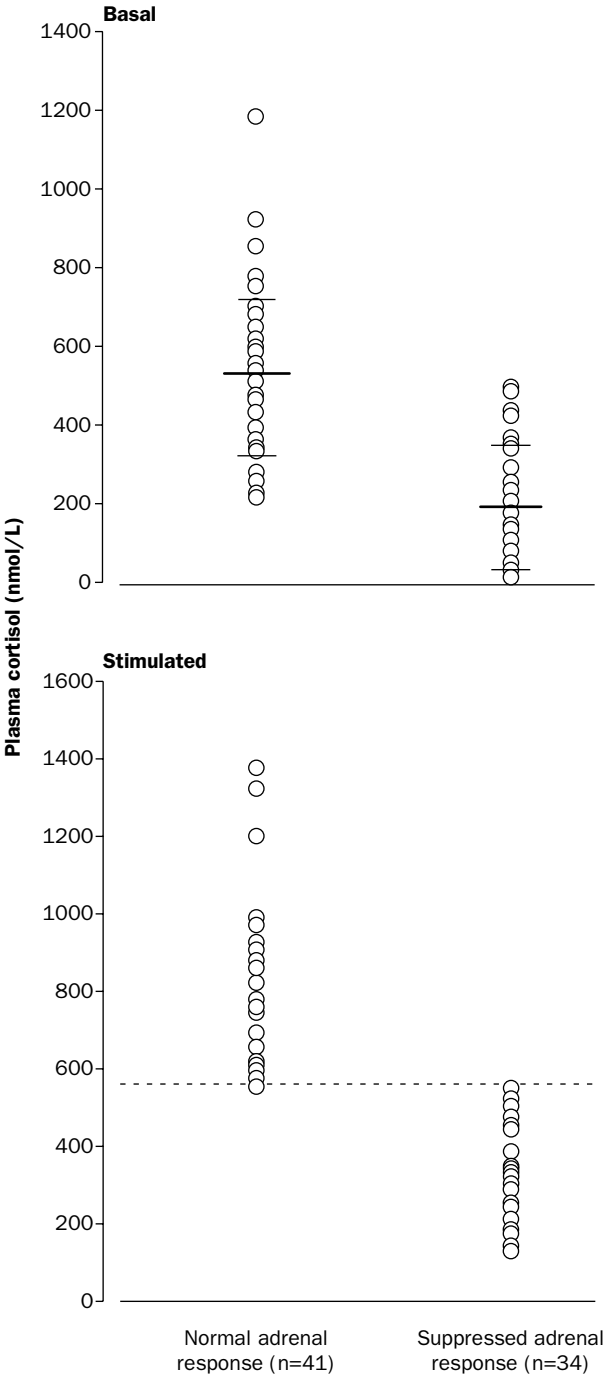
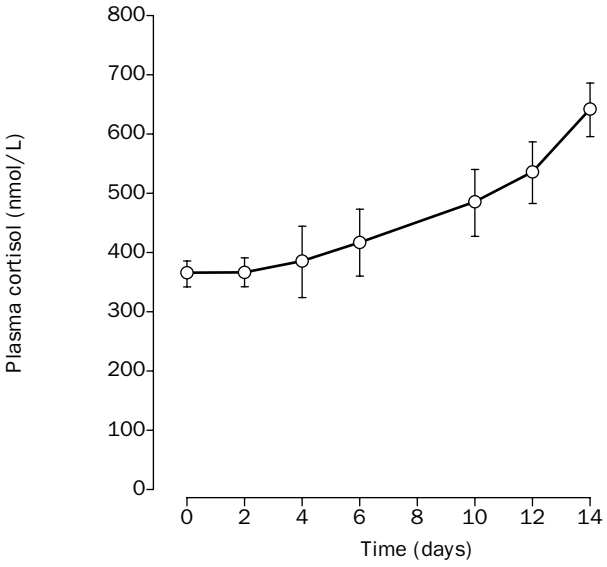


Figure 1: **Basal and stimulated plasma cortisol concentrations**

The mean basal plasma cortisol concentration was significantly higher in patients with a normal adrenal response than in patients with a suppressed adrenal response (524 [SD 201] *vs* 189 [156] nmol/L; p<0·0001, Student's *t* test; figure 1), though the concentrations in the two groups overlapped substantially. After the injection of 1 μg corticotropin, the median stimulated plasma cortisol concentrations in patients with a normal adrenal response and in those with a suppressed adrenal response were 740 nmol/L (range 550–1374) and 362 nmol/L (125–543).

The patients with a normal adrenal response and those with suppressed reponses had similar durations of glucocorticoid treatment (median 8 [range 5–30] *vs* 10 [5–30] days; p=0·60) and similar median daily doses (64 [33–235] *vs* 95 [29–247] mg; p=0·31) and cumulative



Number of patients							
Normal adrenal response	0	0	13	14	21	29	32
Suppressed adrenal response	34	34	21	20	13	5	2

Figure 2: **Results of repeated low-dose corticotropin tests in the 34 patients with suppressed adrenal responses after short-term, high-dose glucocorticoid treatment**
Mean stimulated plasma cortisol concentrations; error bars are SE.

doses (600 [235–5027] *vs* 742 [150–2910] mg; p=0·16) of prednisone. There was no correlation between stimulated plasma cortisol concentrations and duration of glucocorticoid treatment (r=0·08, p=0·46), or the daily (r=0·10; p=0·37) or cumulative (r=0·01; p=0·87) dose of prednisone.

The results of the repeated low-dose corticotropin tests in the 34 patients with suppressed adrenal responses after glucocorticoid treatment are shown in figure 2. In two patients, the stimulated plasma cortisol concentrations on day 14 were less than 550 nmol/L, and their adrenal response to 1 μg corticotropin remained suppressed even at 3 months and 6 months.

Discussion

Function of the adrenal response in patients treated with glucocorticoids shows little correlation with the dose and duration of glucocorticoid treatment, and a random plasma cortisol concentration does not reliably assess the adequacy of the adrenal response to stress.[3–5,19] Therefore, stimulation tests are used in the assessment of the adrenal response;[7] the insulin-induced hypoglycaemia test, the metyrapone test, and the corticotropin-releasing hormone test are considered accurate.[3,6,14,20] However, some of these tests are expensive, physician-intensive, and best done in an endocrine unit, whereas others are contraindicated in some patients.[7] Therefore, the conventional short corticotropin (250 μg) test is widely used.[16,21] In patients with pituitary insufficiency, the lack of continuous trophic stimulation by endogenous corticotropin leads to adrenocortical atrophy and low responsiveness to exogenous corticotropin.[2,15] However, the conventional short corticotropin (250 μg) test as an indirect measurement of the adrenal response induces supraphysiological corticotropin concentrations, giving false-normal cortisol responses and low sensitivity in identifying acute-onset adrenal insufficiency.[7,12,22,23] Results of the low-dose (1 μg) corticotropin test[8,11,12] correlate well with those of the reference test for the function of the adrenal response in patients with pituitary disease.[10,15,18] A single plasma cortisol concentration measured 30 min after the administration of 1 μg corticotropin reliably reflects adrenal function without false-positive results,[17,18,24] although the sensitivity of the low-dose corticotropin test in patients with very recent pituitary insufficiency is disputed.[25]

We confirmed that with the low-dose corticotropin test, neither the duration of treatment nor the daily or cumulative doses of prednisone were associated with adrenal-response deficiency. Both basal and peak plasma cortisol concentrations were significantly lower in patients with deficient than in patients with normal adrenal responses. Apart from blood glucose concentration, there were no other significant differences between patients with normal and suppressed adrenal responses. In patients with suppressed adrenal responses, gradual recovery of function could be demonstrated over a period of 14 days. In two patients the adrenal responses remained suppressed after 3 months and 6 months.

Cortisol has vital circulatory effects in stress responses, and even a mild adrenal insufficiency can be hazardous in critical illness.[26] Symptoms and signs of acute adrenal crisis (ie, dehydration, fever, confusion, nausea, abdominal pain, hypoglycaemia, hypotension, and shock) may occur in such patients exposed to infection, trauma, or surgery. In acutely ill patients, parenteral administration of hydrocortisone should be instituted as soon as the diagnosis of addisonian crisis is suspected. There is evidence that the low-dose corticotropin test enables accurate assessment of adrenocortical function,[15] for example, revealing mild adrenal insufficiency in patients taking inhaled corticosteroids.[9] After long-term glucocorticoid treatment, recovery of the suppressed adrenal response may take more than a year.[5] However, there is substantial individual variation,[2,27] and other factors may be involved, leading to delayed recovery of higher centres.[4,28,29] In our patients, with a median duration of glucocorticoid treatment of less than 12 days, the low-dose corticotropin test revealed a suppressed adrenal response in a surprisingly high proportion (45%). Similar proportions have been reported from studies of patients on long-term glucocorticoid treatment.[3,5] Our patients had a gradual and steady recovery of the suppressed adrenal response to the low-dose corticotropin test within a few days, in contrast to patients on long-term glucocorticoid treatment. The low-dose corticotropin test detected a suppressed adrenal response even in patients who received glucocorticoid treatment for only 5 days.

We conclude that suppression of the adrenal response is common after short-term, high-dose glucocorticoid treatment. In almost all patients with suppressed adrenal response the response to 1 μg corticotropin returned to normal by 2 weeks after the discontinuation of the glucocorticoid treatment. However, during this period of recovery the function of the adrenal response to stress may still be impaired. In a minority of patients the adrenal response may even remain suppressed for several months.

Contributors
Christoph Henzen and Verena Briner designed the study. Alex Suter, Erika Lerch, and Christoph Henzen recruited the participants, organised visits, and did clinical examinations. Ruth Urbinelli did the laboratory tests. Xaver Schorno prepared the corticotropin solution and assessed the

reliability of the technique. Christoph Henzen, Alex Suter, Erika Lerch, and Verena Briner wrote the initial drafts, and all investigators contributed to the final paper.

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