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Salivary Cortisol in Steroid treated Children with Acute Lymphoblastic Leukemia.

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Aim of the Study:

To evaluate the effects of high-dose prednisolone on adrenal function during treatment for acute lymphoblastic leukemia (ALL) by measuring salivary cortisol in comparison with serum cortisol.

Background:

Steroid related side-effects on adrenal function are not well described in these patients and steroid coverage during acute stress has not been routinely used (1). Salivary cortisol reflects the active free form of circulating cortisol, and has the advantage of non-invasive collection convenient for home monitoring (2).

Patients and methods:

Inclusion criteria:

- * Acute lymphoblastic leukaemia (ALL).
- * Age 2 – 16 years
- * No chronic diseases
- * No steroid treatment at inclusion

24 children (17 boys), aged 2-14 (mean 7 years) were prospectively included at diagnosis. All patients received standard induction chemotherapy according to the NOPHO-92-ALL protocol. The prednisolone dosage was 60mg/m² per day for 5 weeks, tapering over 9 days.

Adrenal function was assessed by morning salivary cortisol, and by a low-dose (1:g) ACTH stimulation test, which seems to be a more sensitive screening test of adrenal suppression (3).

4 children, aged 2.5-4.5 years did not accept salivary collection.

Flowchart:

	5 weeks	9 days	day*1	day*3	day*5
Prednisolone 60 mg/m²					
Gradual withdrawal					
ACTH test	x		x	x	x
Morning salivary cortisol			x	x	x
*1, 3, and 5 days posttreatment					

ACTH test: Blood samples and salivary samples were collected just before and 30 minutes after injection of 1 ml of a freshly prepared solution of 250 µg Synacthen® diluted into 250 ml sterile saline solution (1 µg/ml). Central venous catheter was used. A normal response was defined as a peak s-cortisol level > 500 nmol/l and peak salivary cortisol >12 nmol/l. S-cortisol was measured by an immunoassay from ADVIA Centaur System from Bayer.

ACTH tests were performed before initiation of prednisolone therapy, at **baseline**, and repeated **1, 3, and 5 days after** completion of prednisolone therapy.

Salivary measurement: Salivary samples were collected using the Salivette system from Sarstedt, centrifuged and frozen at -20 degrees C until measured by radioimmunoassay employing commercial reagents from Diagnostic Systems Laboratories, inc. Mean (range) morning salivary cortisol in a **control group** of healthy children was 11.5 (1.3-27.7) nmol/l. The value of 12 nmol/l for the lower limit of a normal stimulated cortisol in saliva was chosen as all patients tested at baseline had a normal stimulated s-cortisol > 500 nmol/l and a stimulated cortisol in saliva > 12 nmol/l.

Results:

- * An ACTH test was performed in 13 patients at baseline, and in 17, 15, and 17 patients, respectively, 1, 3, and 5 days after prednisolone therapy.
- * All patients had normal response at baseline.
- * Insufficient serum cortisol response was found in 16 of 17 patients on day 1, and in 8 of 17 patients on day 5 (Fig 1).
- * Insufficient salivary cortisol response was found in 14 of 15 patients on day 1, and in 6 of 15 patients on day 5 (Fig 2)
- * A correlation coefficient of $r^2 = 0.59$ between log salivary cortisol and s-cortisol indicates a positive linear correlation (Fig 3).
- * Morning salivary cortisol levels (mean,range)were suppressed even on day 5 at 5.5 (1.1-16) nmol/l (Fig 4)

Fig 1

Basal and peak s-cortisol values (nmol/l) during ACTH tests in each patient at baseline and 1, 3, and 5 days after steroid treatment.

Fig 2

Basal and peak salivary cortisol values (nmol/l) during ACTH tests at baseline and 1, 3, and 5 days after steroid treatment.

Fig 3

Correlation between time-matched log salivary cortisol and serum cortisol values (nmol/).

Fig 4

Morning and evening salivary cortisol values 1, 3, and 5 days after steroid treatment compared to a control group.

Conclusion:

- * High-dose prednisolone therapy as part of standard treatment for ALL in children can cause adrenal suppression even after tapering the dose over 9 days.
- * The correlation between salivary cortisol and serum cortisol was linear.
- * Home-collected salivary morning cortisol may be a convenient method to assess the adrenal function in a population, but seems to be of less value for individual testing.

References:

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