Suppression of adrenal axis function after high-dose steroid therapy for childhood acute lymphoblastic leukemia in Iran

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ABSTRACT

A 4 weeks course of high-dose glucocorticoids (GCs) may cause prolonged adrenal suppression even after a 9 days tapering phase. In this study, adrenal function and signs and symptoms of adrenal insufficiency were prospectively assessed in children with acute lymphoblastic leukemia (ALL) after induction treatment with high-dose prednisone. In 42 children with newly diagnosed ALL, a baseline serum cortisol level was assessed and after receiving a 28 days of high dose prednisone according to the Berlin-Frankfurt-Münster 2009 protocol ad a 9 days tapering phase, serum cortisol level was assessed again and those whose serum cortisol level was normal underwent low-dose adrenocorticotropic hormone (LDACTH) stimulation 24 h after the last tapered steroid dose. Signs and symptoms of adrenal insufficiency were recorded during the observation period. All patients except one who was excluded had normal basal cortisol values at diagnosis. Twenty-four hours after last GC dose, morning cortisol was reduced in 15 (36.5%) patients. LDACTH testing showed adrenal suppression in 17 (41.4%) patients. High-dose GC therapy in ALL children may cause adrenal suppression even after a tapering phase. Laboratory monitoring of cortisol levels and steroid coverage during stress episodes may be indicated.

Keywords: Adrenal axis function, Steroid therapy, Acute lymphoblastic leukemia

INTRODUCTION

Glucocorticoids (GCs) are an integral component of therapy for pediatric acute lymphoblastic leukemia (ALL) and it is well-known that prolonged corticosteroid therapy and the administration of high doses of GCs (as in the induction phase of Berlin-Frankfurt-Münster (BFM) protocols) can suppress the secretion of corticotrophin releasing hormone by the hypothalamus and of adrenocorticotropic hormone (ACTH) by the pituitary gland, resulting in secondary adrenal cortex atrophy and delayed recovery of hypothalamic-pituitary-adrenal (HPA) axis function. The recovery time of the GC-induced inhibition that occurs in the HPA axis after discontinuation of treatment shows considerable individual variation and may take less than 1 week to several months. The abrupt cessation of steroid therapy may precipitate symptoms of adrenal insufficiency or adrenal crisis during stress. The symptoms, including headache, lethargy, nausea, fever and even abrupt fall in blood pressure are non-specific and often misleading. On the other hand, children with ALL have a significant treatment-related mortality rate as the result of infection, and corticosteroid-induced adrenal insufficiency could be an important contributing factor. As a result, in order to reduce these signs and symptoms, a tapering phase of GC treatment is used in some protocols for ALL.

Unfortunately, little information is known on the occurrence and duration of HPA axis suppression, and it is still not determined that how much and at what rate steroids should
be tapered.\textsuperscript{16,17} In order to show that even the 9 days steroid tapering schedule in BFM-2009 protocol, which we currently use\textsuperscript{15} for childhood ALL could be too short to prevent the mentioned symptoms,\textsuperscript{17} in the current prospective study we assessed adrenal axis function by means of low dose ACTH (LDACTH) testing in children with acute lymphoid leukemia (ALL) after tapering GC therapy.

**METHODS**

In the 1 year period, 42 children with newly diagnosed ALL were consecutively enrolled in the study. The study protocol adhered to the Helsinki declaration and was approved by the Ethics Committee of the Faculty of Medicine, St. Aliaqsaar Hospital, Iran Medical University. Informed consent was obtained from parents. Thus, the study series consisted of 42 children (23 boys, 19 girls), ages 1.5-16 years (mean, 6.4 ± 3.7 years). None had received corticosteroid therapy for other disorders.

All patients received standard induction therapy consisting of prednisolone, vincristine, L-asparaginase, doxorubicin, intra thecal methotrexate according to the induction phase of BFM-2009 protocol.

Each patient received a 28 days course of prednisolone (30 mg/m\textsuperscript{2}/day for the first 7 days and 60 mg/m\textsuperscript{2}/day for the rest in three divided doses) as part of induction therapy, with gradual tapering over a 9 days period after 28 days.

Baseline HPA axis function was assessed by determination of serum cortisol level at 8 a.m. before induction therapy by an electrochemiluminescence method. The normal reference range for the 8 a.m. cortisol level was above 180 nmol/L and hence one of the patients with lower than 180 nmol/l baseline cortisol level was excluded from the study.

Within 24 h after the last tapering dose of prednisolone (on day 38) at 8 a.m. after an overnight fast, baseline serum cortisol level (t-0) was again assessed and adrenal function was tested by using the LDACTH stimulation test.\textsuperscript{17} as follows: A 250 mg ampoule of synaehctin was injected intramuscularly as a bolus. Blood samples for cortisol measurements were withdrawn at 30 min after injection (t-30). A normal response was defined as a stimulated serum cortisol >500 nmol/L.

All participants were evaluated for symptoms such as low blood pressure, fatigue and malaise, lethargy, headache, vomiting and fever from the day 28 (onset of tapering) every 3 days until the day 52 (2 weeks after discontinuation) and their signs and symptoms were documented.

As some studies have demonstrated that adrenal suppression could happen after high-dose fluconazole therapy\textsuperscript{18,19} we did not administer fluconazole to any of our cases during the induction phase.

Chi-square and Fisher’s exact tests were used selectively to compare categorical data where appropriate. Statistical analyzes were performed using the SPSS software version 19.0. \( p < 0.05 \) were considered statistically significant.

**RESULTS**

At diagnosis, basal cortisol values were within the normal range (>180 nmol/l) in all patients but one who was excluded from the study. The serum cortisol level after discontinuation of treatment (t0) was lower than 180 nmol/l in 15 patients (36.6%). At the LDACTH test cortisol levels were <500 nmol/l in 3 of the patients whose baseline cortisol level were normal.

The prevalence of signs and symptoms is revealed, but no significant correlation was found between the patients’ signs and symptoms and their cortisol levels.

Interestingly, serum cortisol levels were higher in female patients before and also after ACTH test.

**DISCUSSION**

Hypothalamo–pituitary–adrenal axis suppression is a potential adverse effect of high-dose administration of GCs depending on the dosage, duration and type of corticosteroid used.\textsuperscript{20} A systematic review conducted by Gordijn et al. demonstrated that adrenal insufficiency occurs in nearly all patients in the 1\textsuperscript{st} day after cessation of GC treatment for childhood ALL.\textsuperscript{21}

Adrenal suppression after administration steroids in children and adults with cancer was first reported by Spiegel et al.,\textsuperscript{22} who found that suppression was independent of dosage and duration and lasted more than 7 days in 5 (36%) of 14 patients.

Lightner et al.\textsuperscript{23} studied 13 ALL patients using prednisone (2 mg/kg/d) for 1 month. Baseline cortisol concentration inhibition was seen 36 h after abrupt GC withdrawal, with eventual recovery 9 d later. No tapering was used in this study.

In 2004, Cunha et al.\textsuperscript{24} evaluated the inhibition of the HPA axis by dexamethasone in children and adolescents with acute lymphoid leukemia, the protocol they used included dexamethasone (6 mg/m\textsuperscript{2}/day, twice daily) given for 28 days plus 9 days’ tapering doses, the time of steroid use and tapering was the same as our study, but the type of steroid was different. In this study, 77% of the patients had suppressed level of cortisol that was much more than what we had in our study (41%).

Other studies conducted by Felner et al.\textsuperscript{25} and Kuperman et al.\textsuperscript{26} which used dexamethasone, did not use tapering so could not be compared with our study. Petersen et al.\textsuperscript{27} studied 17 ALL children after receiving prednisolone (60 mg/m\textsuperscript{2}/d for 5 week) during remission induction, and/or dexamethasone (10 mg/m\textsuperscript{2}/day for 3 week) during reinduction therapy. They also used a 9 days tapering phase before cessation of the steroid, but they did not assess the...
adrenal function immediately after drug cessation. However, in their study, adrenal function remained suppressed in 70% of the patients 1 week after GC withdrawal evaluated by an ACTH stimulation test. This result is also much higher than what we indicated in our study.

In 2005, Rix et al.\textsuperscript{28} according to the NOPHO ALL-92 protocol, administered prednisolone (60 mg/m²/day, in 3 daily doses) during the first 5 weeks of induction therapy followed by 9 days of tapering. LDACHT stimulation test was conducted on day 1 after drug cessation; 94% of the patients had adrenal suppression.

Our study shows that about 41% of children with ALL developed adrenal suppression after a 4 weeks induction therapy with prednisolone and even after gradual tapering of GCs over a 9 days period adrenal suppression could continue to exist. This is potentially life-threatening and so steroid coverage during stressful conditions may be advisable, especially during the first 1-2 months after discontinuation of the steroid.

REFERENCES


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