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Predicting the neurobehavioral side effects of dexamethasone in pediatric acute lymphoblastic leukemia

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ABSTRACT

Although dexamethasone is an effective treatment for acute lymphoblastic leukemia (ALL), it can induce a variety of serious neurobehavioral side effects. We hypothesized that these side effects are influenced by glucocorticoid sensitivity at the tissue level. We therefore prospectively studied whether we could predict the occurrence of these side effects using the very low-dose dexamethasone suppression test (DST) or by measuring trough levels of dexamethasone. Fifty pediatric patients (3–16 years of age) with acute lymphoblastic leukemia (ALL) were initially included during the maintenance phase (with dexamethasone) of the Dutch ALL treatment protocol. As a marker of glucocorticoid sensitivity, the salivary very low-dose DST was used. A post-dexamethasone cortisol level <2.0 nmol/L was considered a hypersensitive response. The neurobehavioral endpoints consisted of questionnaires regarding psychosocial and sleeping problems administered before and during the course of dexamethasone (6 mg/m^2), and dexamethasone trough levels were measured during dexamethasone treatment. Patients with a hypersensitive response to dexamethasone had more behavioral problems (N = 11), sleeping problems, and/or somnolence (N = 12) ($P < 0.05$ for all three endpoints). The positive predictive values of the DST for psychosocial problems and sleeping problems were 50% and 30%, respectively. Dexamethasone levels were not associated with neurobehavioral side effects. We conclude that neither the very low-dose DST nor measuring dexamethasone trough levels can accurately predict dexamethasone-induced neurobehavioral side effects. However, patients with glucocorticoid hypersensitivity experienced significantly more symptoms associated with dexamethasone-induced depression. Future studies should elucidate further the mechanisms by which neurobehavioral side effects are influenced by glucocorticoid sensitivity.

1. Introduction

Dexamethasone is a key drug used in the treatment of pediatric acute lymphoblastic leukemia (ALL) (Balis et al., 1987; Kamps et al., 2000; Veerman et al., 2009); however, its side effects can significantly reduce the patient's quality of life (McGrath and Pitcher, 2002; Hochhauser et al., 2005; van Litsenburg et al., 2011). In the Dutch ALL treatment protocols, medium-risk ALL patients receive three weekly cycles consisting of five-day standard-dose dexamethasone courses during the 1.5-year maintenance period. The reported prevalence of dexamethasone-associated neurobehavioral side effects in pediatric ALL patients varies widely, from 5%

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to as high as 75% (Brown and Suppes 1998; Hochhauser et al., 2005; Stuart et al., 2005). In some cases, these side effects are so severe that dexamethasone treatment is either discontinued or replaced with prednisolone, despite the negative effect on outcome. Therefore, the ability to pre-identify patients at risk for developing neurobehavioral side effects would enable clinicians to offer individualized treatment, potentially reducing the occurrence of dexamethasone-induced side effects (Warris et al., 2016). However, tools for accurately predicting dexamethasone-induced neurobehavioral side effects are not currently available.

Corticosteroids bind to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) and suppress the production of cortisol via a negative feedback loop that acts on the hypothalamus-pituitary-adrenal (HPA) axis (Lustig, 2002). This imbalance in the activation of GRs and MRs caused by the presence of exogenous glucocorticoids in the brain seems to play an important role in the pathophysiology of neuropsychological side effects (de Kloet, 2014). Previous studies indicate that although sensitivity of the GR seems to vary among patients, each patient's sensitivity is relatively stable. This notion is supported by the finding that baseline levels of plasma cortisol—which are regulated by a GR-dependent feedback system—vary widely among healthy individuals but are highly stable within individuals (Huizenga et al., 1998).

The HPA axis' sensitivity to glucocorticoids can be measured using the very low-dose dexamethasone (0.25 mg) suppression test (DST). Baseline cortisol levels represent the individual set point of endogenous cortisol secretion, as they are dependent on the sensitivity of the negative feedback system for endogenous cortisol, but the DST represents the sensitivity for dexamethasone. In population-based studies, subjects with the highest baseline cortisol concentrations had the highest post-DST cortisol concentrations. Moreover, within an individual subject, the specific set point of HPA activity can be measured either before or after a low dose of dexamethasone is administered. A dose of 0.25 mg dexamethasone, which causes the complete suppression of cortisol levels, does not affect this set point. Using the 0.25 mg DST, post-DST cortisol levels have a Gaussian distribution, and subjects at either extreme are relatively hypersensitive or resistant to glucocorticoids (Huizenga et al., 1998).

In addition to differences in glucocorticoid sensitivity, variations in pharmacokinetics may also explain the inter-individual differences with respect to dexamethasone-related side effects. For example, the dexamethasone clearance rate in pediatric ALL patients is inversely correlated with age (Kawedia et al., 2011). Moreover, poor dexamethasone clearance has been reported in ALL patients with osteonecrosis, another serious side effect of dexamethasone treatment (Kawedia et al., 2011). However, whether the pharmacokinetics of dexamethasone also affects the risk of neurobehavioral side effects remains unknown.

The aim of our study was to measure the value of using the very low-dose DST to predict susceptibility to dexamethasone-induced neurobehavioral side effects. In addition, we investigated whether dexamethasone serum levels are correlated with the occurrence of dexamethasone-induced neurobehavioral side effects in pediatric ALL patients.

2. Materials and methods

2.1. Participants

Children (3–6 years of age) with ALL who were enrolled in the Dexadays study (NTR3280), a multicenter randomized controlled trial (Warris et al., 2015), were included. In accordance with the DCOG ALL protocols, each patient was receiving 5-day dexamethasone pulses (6 mg/m^2/day) every three weeks during the maintenance phase. The part of the maintenance phase in which our study was conducted consists of consecutive 21-day treatment cycles in which the patient receives five consecutive days of dexamethasone treatment, one vincristine treatment (on the first day of each cycle), 6-mercaptopurine daily, and methotrexate once per week (Warris et al., 2016). Measurements were performed both before and during the placebo course of the Dexadays study. The study protocol was approved by the local ethics committee (MEC-2012-155/EudraCT 2011-003815-46). The study was performed in accordance with the Declaration of Helsinki and followed the principles of good clinical practice. All participating subjects provided written informed consent.

2.2. Cortisol measurements

The very low-dose salivary dexamethasone suppression test (DST) was performed in the week before a dexamethasone pulse was administered. Measuring salivary cortisol levels is a reliable, minimally invasive method for quantifying the active, unbound form of cortisol (Kirschbaum and Hellhammer, 1994). After receiving detailed oral and written instructions regarding saliva sampling, the patients were instructed to collect saliva samples at home using the Salivette sampling device (Sarstedt, Rommelsdorf, Germany). On two consecutive days, a total of five saliva samples were collected at the following times: immediately upon waking (T1, baseline), at noon (T2), at 4 pm (T3), in the evening at bedtime (T4), and immediately upon waking on the following morning (T5). After obtaining the T4 sample on the first day, a very low dose of dexamethasone (0.25 mg/1.73 m^2) was taken orally. The parents were instructed to write down the exact times and dates that the saliva samples were obtained. Furthermore, the children were instructed to not brush their teeth or eat 15 min before saliva sampling in order to avoid contaminating the saliva. Besides these restrictions, the children were otherwise free to follow their normal daily routines on the sampling days. Parents were instructed to store the saliva samples in the refrigerator until all five samples were obtained. Thereafter, the samples were sent to the Diagnostic Endocrinology Laboratory at Erasmus MC (Rotterdam, the Netherlands), where they were stored at −80 °C until analysis. Cortisol concentration was measured using a commercial chemiluminescence-based immunoassay (CLIA; IBL Hamburg, Hamburg, Germany). The assay's lower limit of detection was 0.4 nmol/L (Erasmus MC, 2015). Data were screened for the quality of cortisol measurements. Saliva samples were used to measure the cortisol day curve (samples T1 through T4) and post-DST cortisol (T5) levels. The HPA axis response was measured by comparing the two morning cortisol levels (i.e., T1 and T5) during the DST.

The area under the curve (AUC) for the cortisol day curve was calculated by the linear trapezoidal method.

Pronounced cortisol suppression was defined as a post-DST (T5) cortisol level <9.0 nmol/L; this was based on the reference value obtained from the Endocrinology Department at Erasmus MC (Erasmus MC, 2015). Severe cortisol suppression was defined as a post-DST cortisol level <2.0 nmol/L. This cut-off value was based on the Guidelines for Cushing Syndrome established by the Endocrine Society (2008) which recommends using a cut-off for suppression of the post-DST (with 1 mg dexamethasone) of <50 nmol/L in order to achieve high sensitivity. Because serum cortisol levels are approximately 27-fold higher than salivary cortisol levels (Reynolds et al., 1998), we chose 2.0 nmol/L as our cut-off value for severe post-DST cortisol suppression.

2.3. Dexamethasone pharmacokinetics

Dexamethasone trough levels were measured after four full days of dexamethasone treatment (6 mg/m^2/day). Serum samples were