High incidence of adrenal suppression in children with Kawasaki disease treated with intravenous immunoglobulin plus prednisolone

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Abstract. Combination treatment with intravenous immunoglobulin (IVIG) plus prednisolone, newly designed for children with severe Kawasaki disease (KD), reduces coronary artery abnormalities significantly. As prednisolone is administered for approximately 20 days in this regimen, we examined whether adrenal function of the treated patients is suppressed. A prospective study was performed at one medical institution in 21 children with KD (age range 0.3-10.4 years, median 3.1 years) who were treated with the regimen between February and June, 2012. We assessed cortisol and ACTH values before the initiation and after the cessation of prednisolone administration as well as peak cortisol and ACTH values at corticotropin-releasing hormone (CRH) stimulation tests, which were repeated 0, 2, and 6 months after the treatment. Morning cortisol and ACTH values after the cessation of prednisolone treatment were suppressed. Peak cortisol values at the first CRH stimulation test ranged from 5.1 to 25.4 µg/dL and were less than 20 µg/dL in 17 of 21 patients, but were restored to more than 14.6 µg/dL in all patients by 6 months after the prednisolone treatment. A significant positive correlation was observed between cortisol values at 09:00 h after the prednisolone treatment and peak cortisol values at the following CRH stimulation test \((r = 0.727, p < 0.001)\). We conclude that adrenal suppression can occur in a high proportion of children with KD treated with IVIG plus prednisolone, despite rather short duration and relatively small amounts of administered glucocorticoids.

Key words: Adrenal suppression, Prednisolone, Kawasaki disease, CRH stimulation test

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IT IS WELL KNOWN that prolonged use of glucocorticoids is associated with suppression of the hypothalamic-pituitary-adrenal (HPA) axis [1]. The degree of HPA axis suppression may be influenced by factors including the dose and duration of glucocorticoid administration. However, there are conflicting descriptions about this. A major review emphasized that glucocorticoid therapy of less than 3 weeks in duration does not cause adrenal suppression, regardless of the administered dose, and that glucocorticoids can be stopped abruptly [2]. Others described that even short courses of glucocorticoids can cause transient adrenal suppression [3-6] and that HPA axis suppression cannot be estimated from the dose or the duration of glucocorticoid therapy [7, 8]. The discrepancy in these reports may arise from the heterogeneity of the recruited patients [7, 8] and the different timings of the assessment [3-8].

Combination treatment with intravenous immunoglobulin (IVIG) plus prednisolone is a newly designed regimen to treat children with severe Kawasaki disease (KD) [9]. It is reported to reduce coronary artery abnormalities significantly [9]. This favorable result may lead to an increasing number of children being treated with this regimen in Japan and other countries. Prednisolone is usually administered for approximately 20 days in the regimen. However, the residual adrenal function of treated children has not been studied. Here, we report that IVIG plus prednisolone therapy can cause adrenal suppression in a high proportion of...
treated children and that recovery from this suppression will occur within 6 months after the prednisolone treatment.

**Subjects and Methods**

**Patients**

This is a prospective study of patients from one medical institution. In the period from February to June 2012, 56 children were newly diagnosed with KD and initiated treatment in our hospital. Among them, 22 children with a risk score of five points or higher for coronary artery complications [10] were treated with IVIG plus prednisolone and enrolled in this study. One girl was excluded as she was administered prednisolone for approximately 2 months in total with some intervals because of her poor clinical response to the initial treatment. The remaining 21 children (13 boys and 8 girls), aged 0.3 to 10.4 years (median 3.1 years), were analyzed. Their body weight ranged from 7.4 to 50 kg (median 12.7 kg). The duration of prednisolone therapy ranged from 16 to 26 days (median 22 days). The cumulative dose of administered prednisolone was 407 to 922 mg/m$^2$ (median 664 mg/m$^2$), which is equivalent to 1,626 to 3,688 mg/m$^2$ (median 2,656 mg/m$^2$) of cortisol (conversion of prednisolone to cortisol is calculated as 4:1).

**Methods**

On the day of admission, blood samples were collected from the enrolled patients for the measurement of cortisol and ACTH at random hours depending on the timing of their arrival at our hospital before the initiation of prednisolone treatment. Subsequently, the patients were given IVIG at a dose of 2 g/kg in approximately 24 hours plus prednisolone at an initial dose of 2 mg/kg/day for more than 5 days, followed by 10 days of tapering periods (Fig. 1) [9]. At the end of the regimen, the prednisolone treatment was switched to cortisol coverage at a dose of 8-10 mg/m$^2$/day in three divided doses to minimize the residual effect of the long-acting prednisolone. Before and 4-8 days after the initiation of cortisol coverage, blood samples were collected for the measurement of cortisol and ACTH at 09:00 h before the daily administration of cortisol (Fig. 1). The patients had the first (0 month) corticotropin-releasing hormone (CRH) stimulation test within 12 days after the last collection of the blood samples (Fig. 1).

After overnight fasting, human CRH (manufactured by Tanabe Mitsubishi Corporation) was administered intravenously at a dose of 1.5 micrograms/kg (max. dose: 100 micrograms) at approximately 09:30h with blood samples drawn 0, 15, 30, 60, 90, and 120 minutes after CRH administration for the measurement of serum cortisol and ACTH concentrations.

Patients with peak serum cortisol concentrations of 20 µg/dL or higher were considered as normal responders [7] and cortisol coverage was stopped at this point. Patients with peak cortisol levels between 10 and 20 µg/dL were considered as partial responders. They also stopped taking daily cortisol at a physiologic dose, but continued to take it at a dose of 80-100 mg/m$^2$/day in the event of severe stress (mostly febrile episodes). Patients with peak cortisol levels less than 10 µg/dL were considered as poor responders and continued to take daily cortisol at a physiologic dose. The dose was increased to 80-100 mg/m$^2$/day in the event of severe stress. CRH stimulation test was repeated in partial and poor responders at 2 and 6 months after the prednisolone treatment. The number and proportion of normal responders were calculated at each period. The proportion of patients with peak cortisol values of 13.1 µg/dL or higher was also calculated, as one report suggests that the normal range of peak cortisol values in children is 13.1-35.6 µg/dL [11].

Serum cortisol concentrations were measured using ARCHITECT Cortisol (Abbott Japan, Chiba). The sensitivity of the assay was 1 µg/dL. Intra-assay and total variations were 2.1-5.5% and 2.5-7.7%, respectively. Serum ACTH concentrations were measured using ECLusys kit ACTH (Roche Diagnostics, Tokyo). The sensitivity of the assay was 1 pg/mL. Intra-assay and total variations were <10% and <25%, respectively.
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Tisol values (range, 19.6 to 67.9 µg/dL; median 29.7 µg/dL) (Fig. 2A). On the other hand, the simultaneous ACTH values ranged from an undetectable level to 36.1 pg/mL (median 7.7 pg/mL) and were suppressed to undetectable levels in 4 of them (Fig. 2B).

Morning cortisol values one day after the cessation of prednisolone (Day 1) ranged from an undetectable level to 5.9 µg/dL (median, undetectable level) and were suppressed to undetectable levels in 16 of them (Fig. 2A). The simultaneous ACTH values ranged from an undetectable level to 5.1 pg/mL (median, undetectable level) and were suppressed to undetectable levels in 13 of them (Fig. 2B). After the coverage of cortisol for 4-8 days, increased ACTH values (Day 5-9) ranged from an undetectable level to 34.6 pg/mL (median 11.7 pg/mL) (Fig. 2B). However, simultaneous cortisol values remained below the normal range (median, 2.1 µg/dL; range, undetectable to 8.4 µg/dL) (Fig. 2A).

Peak cortisol and ACTH values at the following CRH stimulation test (0 months after the prednisolone treatment) were 5.1 to 25.4 µg/dL (median, 11.8 µg/dL) and 23 to 155 pg/mL (median, 40.8 pg/mL), respectively (Fig. 3A, B).

Among the 21 enrolled patients, peak cortisol values at repeated CRH stimulation tests had reached more than 20 µg/dL in 12 (57.1%) and to more than 13.1 µg/dL in all of them by 6 months after the prednisolone treatment (Fig. 3A). In 14 patients who underwent the CRH stimulation test three times, the ranges of peak cortisol values at 0, 2, and 6 months after the prednisolone treatment were 13.1 to 25.4 µg/dL (median, 17.7 µg/dL) and 23 to 155 pg/mL (median, 40.8 pg/mL), respectively (Fig. 3A, B).

This study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki, and with the ethical guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare in Japan. The study was approved by the ethics review board of Tokyo Metropolitan Children’s Medical Center (ID: H23-75). Informed consent was obtained from the parents at enrollment.

Statistical analyses

All statistical analyses were conducted with SPSS Statistics 20 (IBM). Continuous variable data are expressed as the range with the median. A non-parametric Mann-Whitney test was used to compare the peak cortisol levels at CRH stimulation test among different periods from the prednisolone treatment (0, 2, and 6 months). To evaluate the correlation between morning cortisol values at 09:00 h after the cortisol coverage and peak cortisol levels at the following CRH stimulation test or between basal and peak cortisol values at the CRH stimulation test, simple linear regression analysis was performed using Spearman’s correlation coefficient. A p value less than 0.05 was taken as an indicator of a significant difference.

Results

Adrenal function at random hours before the administration of prednisolone had been evaluated in 20 of the 21 enrolled patients. All of them had stressed cortisol values (range, 19.6 to 67.9 µg/dL; median 29.7 µg/dL) (Fig. 2A). On the other hand, the simultaneous ACTH values ranged from an undetectable level to 36.1 pg/mL (median 7.7 pg/mL) and were suppressed to undetectable levels in 4 of them (Fig. 2B).

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The morning cortisol values at 09:00 h 4-8 days after the cessation of prednisolone treatment (Days 5-9) showed a significant positive correlation with peak cortisol values at the following CRH stimulation test (0 months) ($r = 0.727$, $p < 0.001$) (Fig. 4). A significant positive correlation was also found between basal and peak cortisol values at the same CRH stimulation test ($r = 0.777$, $p < 0.001$) (Fig. 5).

Peak cortisol values at 2 and 6 months after the prednisolone treatment were 5.1 to 14.2 µg/dL (median 10.2 µg/dL), 12.2 to 19.5 µg/dL (median 15.9 µg/dL), and 14.6 to 25.6 µg/dL (median 20 µg/dL), respectively. Peak cortisol values at 2 and 6 months after the prednisolone treatment were significantly higher than those at 0 months after the treatment (Fig. 3A). Although daily physiologic cortisol coverage was stopped in 13 of them at 0 months and in all of them by 2 months after the treatment based on the peak cortisol values higher than 10 µg/dL, none of the patients showed symptoms of adrenal insufficiency during the following observation period.

There was a significant positive correlation between morning cortisol values at 09:00 h 4-8 days after the cessation of prednisolone treatment (Days 5-9) and peak cortisol values at the following CRH stimulation test (0 months) ($r = 0.727$, $p < 0.001$) (Fig. 4). A significant positive correlation was also found between basal and peak cortisol values at the same CRH stimulation test ($r = 0.777$, $p < 0.001$) (Fig. 5).
Discussion

This study has revealed that adrenal function is suppressed in a high proportion of children with KD treated with IVIG plus prednisolone. Cortisol was suppressed below normal values not only one day after the cessation of prednisolone treatment but also 4 to 8 days after the initiation of cortisol coverage (Fig. 2). Peak cortisol values at the first CRH stimulation test (0 months) were also suppressed in a high proportion of treated children, but increased significantly by 6 months after the prednisolone treatment (Fig. 3A). We also found a significant positive correlation between morning cortisol values 4-8 days after the initiation of cortisol coverage and peak cortisol values at the following CRH stimulation test (Fig. 4).

No definitive threshold of the dose or the duration of glucocorticoid administration that causes adrenal suppression is confirmed in the literature. This is partly because previous reported studies often dealt with a heterogeneous group of subjects with different backgrounds of disease and various schedules of glucocorticoid administration [7, 8]. The various timings or examinations used in the assessment of adrenal function can be another reason [3-8, 12-18]. Our uniform protocol of glucocorticoid administration and evaluation of residual adrenal function in patients with the same background of disease might have avoided these problems. However, we still observed a broad spectrum of residual adrenal function in our patients. This may be explained by various factors such as individual variation in absorption and metabolism of glucocorticoids, and in the secretion of cortisol in response to stimulation tests.

Data of residual adrenal function in children with acute lymphoblastic leukemia have been accumulated. They are usually given prednisolone or dexamethasone for 4-6 weeks [12-18]. The cumulative dose amounts to more than 1,120 mg/m² prednisolone (equivalent to 4,480 mg/m² cortisol) or 168 mg/m² dexamethasone (equivalent to 4,200-13,440 mg/m² cortisol when conversion is calculated as 25-80:1) [19]. Adrenal suppression is reported to occur in most of them. In this study, we showed that adrenal suppression can occur even with administration of a smaller dosage of glucocorticoids. It can also occur even with glucocorticoid administration for less than 3 weeks, which has been considered not to cause adrenal suppression [2].

In contrast, transient adrenal suppression was previously observed in subjects with glucocorticoid administration at an even smaller dosage than in our patients, or even with a single administration of glucocorticoids [3-6]. These descriptions may be compatible with our observation of suppressed cortisol values in all of our patients one day after the cessation of prednisolone treatment. These results may also support our strategy of cortisol coverage after the cessation of long-acting glucocorticoids to avoid acute adrenal insufficiency.

A single estimation of cortisol level at 09:00 h may reflect preserved adrenal function and be a substitute for the CRH stimulation test in patients treated with IVIG plus prednisolone. Previous reports described that a single determination of morning cortisol level reflects basal adrenal function but gives no indication of the capacity to respond to stress [7, 20], suggesting the importance of stimulation tests such as insulin, CRH, and ACTH. Our study showed that cortisol values at 09:00 h are correlated significantly with peak cortisol values in the following CRH stimulation test (Fig. 4). Measurement of cortisol values at 09:00 h, which is later than the standard sample collection at 06:00-08:00 h, may be a useful tool for screening patients with adrenal suppression by lowering the cut-off values.

For many institutions where CRH stimulation tests are difficult to perform, we propose prescribing both daily physiologic cortisol and high-dose cortisol in the event of severe stress after the cessation of prednisolone treatment. Cortisol values at 09:00 h should be examined at 5 days, 2 months, and 4 months after the treatment. Physiologic cortisol and high-dose cortisol therapy should be stopped when cortisol values at 09:00 h exceed 2.5 µg/dL and when cortisol values at 09:00 h exceed 5 µg/dL, respectively. Irrespective of the past cortisol values, both therapies will be discontinued 6 months after prednisolone treatment. However, less strict protocol is possible as their adrenal suppression is subclinical.

The potency of morning cortisol values as a substitute for CRH stimulation test may be limited to this population only. Significant positive correlation between morning cortisol values and peak cortisol values at the following CRH stimulation test in this population may be attributed to their homogeneous backgrounds, namely the same regimen, a rather homogeneous dose and duration of steroid administration [9]. We are skeptical about the application of the same approach to other population treated with higher doses and longer duration of glucocorticoid.

We cannot rule out the possibility that the cortisol
coverage after the cessation of prednisolone treatment itself may have delayed the recovery of adrenal function. Adrenal function of children with acute lymphoblastic leukemia treated with either prednisolone or dexamethasone without cortisol coverage was reported to recover earlier than in our patients, despite longer duration and higher administered doses of glucocorticoid [15, 17]. However, we consider that cortisol coverage is inevitable to avoid the risk of adrenal insufficiency during the period of adrenal suppression. There are several reports describing the increased risk of fatal adrenal crisis in patients with combined hypopituitarism [21-23] and severe adrenal crisis in those with adrenal insufficiency [24]. Adrenal crisis can occur in these patients even when they are taking a daily maintenance dose of glucocorticoid or even with episodes of trivial infections [21-24]. We also consider that the protocol of cortisol coverage in our study did not have a severe negative effect on the recovery of the adrenal function. It is because daily physiologic cortisol coverage was stopped in 13 of the 21 patients at 0 months and in all of them by 2 months after the treatment.

We are skeptical about the possibility that the IVIG treatment itself may have caused adrenal suppression. Sano et al. measured serum cortisol values in patients with KD repeatedly during the course of IVIG treatment. They reported that mean morning cortisol values of the patients at convalescence after IVIG treatment was about 10 µg/dL [25], suggesting their patients’ adrenal function was reserved.

We also have to reconsider the validity of the normal range applied for peak cortisol values in the CRH stimulation test. Schlaghecke et al. defined a normal response of the CRH stimulation test in adults as a peak cortisol value above 20 µg/dL and patients with lower peak cortisol values were classified as blunted plasma cortisol responders [7]. However, Tanaka et al. suggested that the normal range of peak cortisol values is 13.1-35.6 µg/dL based on data from 38 children with idiopathic short stature [11]. If we use the level of 13.1 µg/dL as a cut-off value, 20 (95.2%) and 21 (100%) of our patients are supposed to have had normal adrenal response by 2 and 6 months after the treatment, respectively (Fig. 3).

In conclusion, adrenal suppression can occur in a high proportion of children with KD treated with IVIG plus prednisolone, despite a rather short duration and relatively small amounts of administered glucocorticoids compared with the protocol of leukemia. The suppressed adrenal function will be restored within 6 months. Adequate assessment and care of their residual adrenal function are needed during this period. Morning cortisol values at 09:00 h may be useful to assess this and have the potential to be a substitute for the CRH stimulation test in this population.

**Disclosure**

None of the authors have any potential conflicts of interest associated with this research.

**References**


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