Effect of multiple courses of antenatal corticosteroids on pituitary-adrenal function in preterm infants

P C Ng, G W K Wong, C W K Lam, C H Lee, T F Fok, M Y Wong, K C Ma

Abstract

Aim—To evaluate the pituitary–adrenal function of preterm infants whose mothers received multiple courses (8 or more doses) of antenatal dexamethasone.

Methods—The pituitary–adrenal function of 14 preterm infants whose mothers received eight or more doses of antenatal dexamethasone were assessed using the human corticotrophin releasing hormone (hCRH) stimulation test when 7 days (n = 14) and 14 days old (n = 12). During each test, blood samples were taken at 0 (baseline), 15, 30 and 60 minutes after an intravenous bolus dose of hCRH (1 µg/kg). The corresponding hormone concentrations were compared between days 7 and 14, and with various associated factors.

Results—The baseline (0 min) plasma adrenocorticotropic hormone concentration was significantly higher at day 14 than at day 7 (p = 0.036). None of the corresponding poststimulation (15, 30, and 60 min) hormone concentrations was significantly different between the two time epochs. When the association between the hormone concentrations and the number of antenatal dexamethasone doses received by the mothers was assessed, a significant negative correlation was observed in serum cortisol concentrations at 15 and 30 min on day 14 (r = −0.59, p = 0.04 and r = −0.60, p = 0.039, respectively).

Conclusions—The absence of a significant difference in poststimulation hormone concentrations between days 7 and 14 in this cohort of infants, and the similarity of their hormone responses with those of older children and adults, suggests that no severe pituitary–adrenal suppression had occurred. None the less there was evidence of mild adrenal suppression in some of the treated infants. Vigilance in monitoring blood pressure, electrolytes and signs of adrenal suppression in infants whose mothers receive multiple courses (8 or more doses) of antenatal dexamethasone is required, as some of them might have diminished adrenal reserve.

Table 1 Clinical characteristics of study population (n = 14)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>32.5 (2.3)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1539 (438)</td>
</tr>
<tr>
<td>Apgar scores 1 min &lt; 7 (n)</td>
<td>3,0</td>
</tr>
<tr>
<td>Number of antenatal doses</td>
<td>10 (8-18)</td>
</tr>
<tr>
<td>Time between the last dose</td>
<td>3-5</td>
</tr>
<tr>
<td>Mode of delivery: vaginal: caesarean section</td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>1:13</td>
</tr>
<tr>
<td>Singleton:twins:triplets</td>
<td>8:0:6</td>
</tr>
<tr>
<td>Inborn:outborn</td>
<td>14:0</td>
</tr>
<tr>
<td>Infants requiring assisted</td>
<td>5,3</td>
</tr>
</tbody>
</table>

Keywords: antenatal dexamethasone; hCRH; pituitary–adrenal; preterm

Antenatal corticosteroids have been widely used for the prevention of respiratory distress syndrome (RDS) and its associated complications in preterm infants. This modality of treatment has become an established part of routine obstetric management in many institutions, but as the effectiveness of the treatment wanes after 7 days, repeated courses of corticosteroids are required to sustain the beneficial effect if the risk of imminent preterm delivery persists or recurs. We have recently studied the influence of antenatal and postnatal dexamethasone on the hypothalamic–pituitary–adrenal (HPA) axis in preterm, very low birthweight (VLBW) infants and our results suggest that infants whose mothers received less than eight doses (4 courses) of antenatal dexamethasone, have no long lasting suppressive effects on the pituitary–adrenal function at day 7 or later. We have also shown that both the pituitary and adrenal glands had substantially recovered 28 days after discontinuation of a three week course of postnatal dexamethasone during which the dose was gradually reduced. As we were unsure whether eight or more doses of antenatal dexamethasone would suppress the HPA axis, a prospective study was performed to investigate the effect of multiple courses (8 or more doses) of antenatal dexamethasone on the pituitary–adrenal function using the human corticotrophin releasing hormone (hCRH) stimulation test.
corticosteroids treatment before the hCRH tests. Infants were excluded if they had concurrent hypoglycaemia, systemic infection, necrotising enterocolitis, or major surgery in the preceding week.

The decision to administer antenatal dexamethasone rested entirely with the attending obstetrician. Management guidelines for starting antenatal dexamethasone treatment in women between 24–34 weeks of gestation were: (i) threatened preterm labour; (ii) antepartum haemorrhage; (iii) preterm rupture of membranes; and (iv) any condition requiring elective premature delivery. Repeated courses were administered weekly if the risk of imminent preterm delivery persisted or recurred after initial treatment. Treatment was to be stopped when the fetus reached 34 weeks of gestation as the risk of developing severe RDS was minimal after this critical period. Each course consisted of two doses of dexamethasone (dexamethasone sodium phosphate; Weimer Pharma, Gmbh, Rastatt, Germany) 10 mg given intramuscularly 12 hours apart.

We performed the hCRH stimulation test following a standard schedule on days 7 and 14. The hCRH test was performed between 0800–1000 hours, as described before. The plasma corticotrophin (ACTH) and serum cortisol concentration were measured by double antibody radioimmunoassay and solid phase radioimmunoassay, respectively.

Ethical approval for the study was obtained from the Research Ethics Committee of the Chinese University of Hong Kong. Informed parental consent was obtained for each case before the start of any test.

Student’s t test was used to compare the corresponding hormone concentrations between days 7 and 14 of postnatal age. Linear regression analysis was used to assess the correlation between the hormone concentrations and various associated factors.

**Results**

Fourteen infants whose mothers received eight or more doses (mean 11.6; median 10; range 8–18 doses) of antenatal dexamethasone were enrolled. The clinical characteristics of the study population are summarised in table 1. Twenty six hCRH stimulation tests were performed in this cohort of infants at days 7 and 14 of postnatal age. Two infants missed the second hCRH test on day 14 as they no longer had an intravascular line. Table 2 and figs 1 and 2 show the mean plasma ACTH and serum cortisol concentrations in response to hCRH stimulation at days 7 and 14.

The baseline (0 min) plasma ACTH concentration was significantly higher at day 14 than at day 7 (p = 0.036). None of the poststimulation (15, 30, and 60 min) plasma ACTH and serum cortisol concentrations at day 14 was significantly different when compared with their corresponding concentrations at day 7 (p > 0.05 and p > 0.15, respectively).

A negative trend was observed when the association between the hormone concentra-
Pituitary–adrenal function in preterm infants after antenatal corticosteroids

There were also no significant differences in poststimulation plasma ACTH and serum cortisol concentrations between days 7 and 14 in the studied population (table 2), providing further evidence that the infants’ HPA axis remained responsive despite multiple courses of antenatal corticosteroids. The higher baseline plasma ACTH concentration at day 14 probably represented the postnatal adaptation of the endocrine axis after birth.8 11

Despite the above findings there was evidence of mild adrenal suppression in infants whose mother received multiple courses of antenatal dexamethasone. A significant negative correlation was observed between the poststimulation serum cortisol concentrations of the infants and the cumulative antenatal dexamethasone doses received by the mothers. Furthermore, three of 26 hCRH tests had peak serum cortisol concentrations < 330 nmol/l, which suggested slight blunting of the adrenal responses. Nevertheless, it was reassuring to note that none of the studied infants developed clinical signs or electrolyte disturbances suggestive of adrenal insufficiency, or required steroid replacement.

In summary, multiple courses (mean 11.6 doses) of antenatal dexamethasone do not cause severe and/or prolonged suppression in neonates at 7 days of age or older. However, a mild degree of adrenal suppression may occur in a small proportion of treated infants. Although the severity of suppression increases with the cumulative dexamethasone dose received by the mothers, the effect does not translate into clinically significant adrenal insufficiency or crisis. We can confidently conclude from our series of studies that a standard course of antenatal dexamethasone has no long lasting suppressive effects on the pituitary–adrenal function in newborn infants. Even multiple courses (mean 11.6 doses) of antenatal corticosteroids have relatively little clinical or biochemical influence on the endocrine axis. However, we urge for vigilance in monitoring blood pressure, electrolytes, and signs of adrenal suppression in all neonates whose mothers have received eight or more doses of antenatal dexamethasone, as some of these infants might have diminished adrenal reserve.

Discussion

One of the most feared adverse effects of antenatal dexamethasone is HPA axis suppression in newborn infants. As this treatment is of confirmed value for the prevention of RDS,1 2 perinatal clinicians are likely to be more liberal in prescribing multiple courses of antenatal corticosteroids to mothers who are at high risk of imminent preterm delivery. However, little is known about HPA axis suppression in preterm infants whose mothers are given eight or more doses. Hence this study was undertaken to investigate in detail the effect on the pituitary–adrenal function in such patients.

A major problem in assessing the adequacy of the pituitary–adrenal response in this cohort of moderately premature infants is the lack of a reference standard against which their hormone responses may be judged.10 It would not be ethical to include a control group by subjecting infants of gestational age 32 weeks or above, who had never received antenatal corticosteroids, to the hCRH stimulation test. Most such patients would not require intravascular line monitoring and their chance of requiring postnatal corticosteroid treatment should be minimal. In the absence of an ideal control group we opted to compare these results with those of our previous work which involved 17 preterm VLBW infants who did not receive antenatal corticosteroids and who had their pituitary–adrenal function assessed by the hCRH test at days 7 and 14 of life.6 Only the 60 min serum cortisol concentration at day 7 was significantly lower in the antenatal corticosteroid treatment group than in the non-treatment group when corresponding doses were compared (mean (SEM) serum cortisol concentrations were 347 (64) and 632 (83) nmol/l, respectively; mean (SEM) differences were 285 (108) nmol/l; p < 0.02). Obviously, such comparison should be interpreted with caution as the demographic characteristics between the two groups of infants were different. None the less it does provide an insight into the HPA function of preterm infants and, more importantly, we did not find any severe pituitary–adrenal suppression in the treated neonates. Furthermore, the configuration of the response curves and the magnitude of the responses (figs 1 and 2) were similar to those observed in older children and adults.11 12

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