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.

(Arch Dis Child Fetal Neonatal Ed 1999;80:F213–F216)

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.

Methods

Fourteen preterm infants were prospectively recruited between August 1994 and December 1997. Inclusion criteria were: (i) infants whose mother received eight or more doses of antenatal dexamethasone during pregnancy; (ii) time interval between the last dose of antenatal steroid and delivery less than 28 days; (iii) presence of an intravascular line at day 7 (a second hCRH test would also be performed if the intravascular line was still in situ on day 14); and (iv) no postnatal inhaled or systemic complications.

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

<table>
<thead>
<tr>
<th>Characteristic</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), 5 min &lt; 7 (n)</td>
<td>3,0</td>
</tr>
<tr>
<td>Number of antenatal dexamethasone doses received*</td>
<td>10 (8-18)</td>
</tr>
<tr>
<td>Time between the last dose of antenatal steroid and delivery (h)§</td>
<td>102 (18-432)</td>
</tr>
<tr>
<td>Mode of delivery: vaginal: caesarean section Male:female</td>
<td>1:13</td>
</tr>
<tr>
<td>Singleton:twins:triplets</td>
<td>7:7</td>
</tr>
<tr>
<td>Inborn:outborn</td>
<td>8:0:6</td>
</tr>
<tr>
<td>Infants requiring assisted ventilation at day 7 (n), at day 14 (n)</td>
<td>14:0</td>
</tr>
</tbody>
</table>

† values are mean (SD); * values are median (range)
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.

<table>
<thead>
<tr>
<th>ACTH (pmol/l)</th>
<th>Cortisol (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
</tr>
<tr>
<td>Day 7 (n = 14)</td>
<td>5.1 (0.7)</td>
</tr>
<tr>
<td>Day 14 (n = 12)</td>
<td>7.9 (1.1)</td>
</tr>
<tr>
<td>Differences between days 14 and 7 (n = 12)</td>
<td>2.4 (1.3)</td>
</tr>
</tbody>
</table>

Values are mean (SEM)
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 concentration in 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 permanent pituitary–adrenal 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 studies7–9 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.

8. Ng PC, Wong GWK, Lam CWK, et al. Pituitary-adrenal response in preterm very low birth weight infants after...


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Arch Dis Child Fetal Neonatal Ed 1999 80: F213-F216
doi: 10.1136/fn.80.3.F213

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