Dexamethasone therapy is associated with a rise in urinary epidermal growth factor concentrations in the preterm infant

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The effect of glucocorticoid hormones on epidermal growth factor (EGF) concentrations has not been described in the premature infant. We examined this relationship in a group of infants treated with dexamethasone for airway edema (three to five doses) or chronic lung disease (six weeks of a tapering protocol). We collected urinary samples in 45 infants (25 for airway edema, 20 for chronic lung disease) before, during and after the use of dexamethasone. The EGF values were unchanged in infants that were given dexamethasone for airway edema. In contrast, all infants treated for chronic lung disease increased their EGF values by 1 week of therapy. At the end of the dexamethasone taper, ten of the infants had recovered successfully from ventilatory support. This group of infants had post-therapy EGF values that were significantly higher than pretherapy values. In the ten infants that were still ventilator dependent at the end of therapy, EGF values were not different from pretherapy values. We conclude that dexamethasone therapy was associated with an increase in urinary EGF values in the preterm infant treated for at least 1 week. The positive correlation of tapering from ventilatory support with increases in EGF values suggests that EGF may be a marker of dexamethasone effect or an effecter of dexamethasone action.

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Epidermal growth factor (EGF) concentrations are increased by exposure to thyroid and growth hormones in both animal and human studies (1–4). Further, perturbations of thyroid function in the premature infant have been demonstrated to affect directly the urinary EGF concentrations (5). The effect of glucocorticoid hormones on EGF concentrations have been studied primarily in relationship to the development of the lung and the adrenal gland (6–8). In both organs, EGF may be necessary for normal differentiation (9) and glucocorticoid hormones appear to work in concert with EGF in these organs (10). It is less clear what the feedback relationship between the factors may be. Glucocorticoid hormones enhance EGF receptor binding under some circumstances (11) and interfere with EGF action under other conditions (12).

The relationship of glucocorticoid hormones to EGF concentrations has not been addressed in the preterm infant. The use of dexamethasone for clinical indications provided a group of infants in whom the effect of dexamethasone on urinary EGF values could be measured. We found that dexamethasone therapy was associated with an increase in urinary EGF concentrations.

Methods

Subjects

All infants in the Newborn Intensive Care Unit at the Children’s Hospital of New Mexico from 1985 through 1989 who received dexamethasone for clinical indications were eligible for this study. Each infant was studied by a human research review committee after approved consent was obtained from the parents or legal guardians. A urine sample was obtained before and 1 week after therapy for all infants and weekly beginning at 1 week for infants treated for greater than 7 days.

A post hoc group was included. This group was matched to the infants treated for chronic lung disease for initial ventilatory settings, sex and gestational age. They served as a comparison group for initial acuity, gender and age.

Ventilatory support was quantified by use of the respiratory acuity score (RAS), which is the whole number sum of $\frac{F_0}{F_0} > 0.25$ (corrected for the effect of altitude), peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP) and number of breaths provided by the ventilator (IMV). This value...
has been correlated positively to blood gas values. An example is: if \( F_1O_2 = 0.40 \), PIP/PEEP = 20/4 and IMV = 30, then RAS = 15 + 20 + 4 + 30 = 69 (13).

Epidermal growth factor assay

All urine samples from an infant were batched for measurement of EGF in the same assay by our RIA method (5). The RIA had an intra-assay variance of 8.0% and an interassay variance of 8.6%. Recovery of EGF was 85%, and human urine displaced hEGF in a parallel fashion. All samples were corrected for recovery. The sensitivity of the assay was 50 pg. Creatinine (Cr) measurements were made by the picric acid method (14). Correction of the EGF values by creatinine were adjusted for the variability of random sampling during a single day. We have demonstrated the usefulness of this correction in full-term infants (15). All samples were measured in duplicate tubes.

Dexamethasone therapy

The clinical criteria for the use of dexamethasone were at the discretion of the attending physician. If dexamethasone was given for presumed airway edema, the dose was 0.5 mg/kg for three to five doses given every 12 h. The use of dexamethasone for chronic lung disease (CLD) followed the criteria defined by Avery et al. (16). All infants were ventilator dependent with \( F_1O_2 > 0.60 \). Dexamethasone sodium phosphate was started at 0.5 mg/kg per day intravenously in two divided doses for 3 days. The dose then was decreased to 0.3 mg/kg per day for 3 days. The dose was decreased further by 10% of the current dose every 3 days until a dose of 0.1 mg/kg per day was reached. The dexamethasone then was given on alternate days for a week and then discontinued.

The EGF values were placed into one of two subgroups defined by the clinical response of the infants to glucocorticoid hormone therapy (responsive and non-responsive group, respectively). Those infants who were tapered off the ventilatory support while on dexamethasone were designated the responsive group. Those infants who were still ventilator dependent at the end of the therapy were placed into the non-responsive group.

Adrenocorticotropic-stimulation test

After adrenal insufficiency was diagnosed in one infant with a 6-week tapering regime, subsequent infants were tested with the ACTH-stimulation test using 3–4 µg/kg Cortrosyn® (17). A blood sample was collected before and 30 min after the Cortrosyn® was given im or iv. There are no well-examined tests of the hypothalamic–pituitary–adrenal (HPA) axis in the preterm infant. The ACTH test is a rapid, safe screening test of the axis frequently used in children and adults. Normal values for the test are not known in the preterm infant. We chose arbitrarily a rise of greater than 138 nmol/l (50 µg/l) as an acceptable response to the test.

Statistics

Paired student t-tests were used for EGF values before and after therapy for infants treated for airway edema; ANOVA analysis was used to compare values before, peak during therapy and after therapy and between the two responsive and non-responsive subgroups, respectively.

Results

Subjects

Forty-five infants were included in the study (20 girl infants and 25 boy infants). There were 25 infants that received dexamethasone for airway edema and 20 infants that received dexamethasone for treatment of chronic lung disease. The ventilatory settings for the comparison group and the treated infants were similar (RAS = 98 ± 16 versus 103 ± 14, respectively) on day 1 of life. Each infant in the treatment groups had been treated for possible sepsis one to three times before dexamethasone therapy was initiated. There was a similar range for the number of treated episodes in the two treatment groups and for the comparison group. There were three infants in the comparison group and seven (four responsive, three non-responsive) groups who were fed human milk as their main source of nutrition, suggesting that human milk as a source of EGF was not a contributing factor to the changes noted for urinary EGF concentrations.

Table 1 displays the clinical characteristics of the treatment groups for CLD. The sex distribution and mean ± SD gestational age were the same for the comparison and the treatment groups. The treatment groups were similar for gender distribution and post-conceptional age at birth. Infants in the non-responsive group were significantly older than infants in the responsive group for post-conceptional and postnatal age (p < 0.01) at the time therapy was begun.

All infants in the responsive group were ventilator independent by 3 weeks of therapy and were discharged home within 1 month of cessation of therapy. In the non-responsive group, eight of ten infants received the 6-week tapering regime. The dosage was increased in two infants during the protocol because of clinical deterioration leading to greater than 6 weeks of therapy. Eight infants in this group died of ventilatory failure while being ventilator dependent. The other two infants were 9 and 12 months old, respectively, at the time when ventilator independence was achieved.
Table 1. Clinical data on treatment groups.\(^a\)

<table>
<thead>
<tr>
<th>Age distribution</th>
<th>Responsive</th>
<th>Non-responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex distribution (girls/boys)</td>
<td>6/4</td>
<td>5/5</td>
</tr>
<tr>
<td>Gestational age (weeks at birth)</td>
<td>28 ± 1</td>
<td>27 ± 1</td>
</tr>
<tr>
<td>Post-conceptional age (at beginning of therapy)</td>
<td>34 ± 1**</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>Postnatal age (at beginning of therapy)</td>
<td>6 ± 1**</td>
<td>12 ± 3</td>
</tr>
</tbody>
</table>

\(^a\) Sex distribution and gestational age were the same for the comparison and treatment groups; \(^**p < 0.01\) for responsive versus non-responsive groups.

**Epidermal growth factor concentrations**

There was no significant change in EGF excretion from baseline to end of therapy for the infants with airway edema (45 ± 14 versus 34 ± 9 \(\mu\)mol EGF/\(\mu\)mol Cr). The EGF values during the first 24 h of life were available from all the comparison groups as well as for five infants in each of the treatment groups CLD. There were no significant differences in the EGF concentrations between the comparison group and treated infants (32 ± 8 vs 30 ± 12 \(\mu\)mol EGF/\(\mu\)mol Cr, respectively).

Pretherapy EGF values were low compared to values from infants treated for airway edema. Therefore, we made a post hoc comparison of the EGF values from the treated infants to a comparison group of infants who recovered from ventilatory support without dexamethasone therapy. The infants were matched for sex, gestational age and magnitude of ventilatory support at birth. The EGF values were matched for the same postnatal age. We included these restrictions on values because previously we have demonstrated significant effects from sex, gestational age and postnatal age on the urinary EGF concentrations (15). We found that the pretherapy EGF values were significantly lower for all treated infants compared to the comparison group.

For both groups treated for CLD, there was a significant increase after 1 week of dexamethasone therapy. The highest concentrations of EGF were at week 1 or 2 for both responsive (\(p < 0.001\)) and non-responsive (\(p < 0.05\)) groups. There was a significant difference in the peak values for EGF between the two groups, while the pretherapy values were not different (\(p < 0.005\)) (Table 2). Values at the end of therapy were increased significantly from pretherapy values in the group of infants who recovered successfully from ventilatory support (\(p < 0.01\)). The non-responsive group had EGF values that were unchanged from pretherapy values. The peak values in the responsive group were significantly higher than the values from the comparison group (\(p = 0.05\)). The post-therapy EGF values were similar for the responsive group (Fig. 1) and the comparison group. For the non-responsive group, post-therapy EGF values were not different from pretherapy values and significantly lower than values from the comparison group (\(p < 0.01\)) (Fig. 2).

**Adrenocorticotropin stimulation test**

After treating nine infants without clinically recognized adrenal compromise, one infant developed symptomatic adrenal insufficiency. She was 2 weeks off the tapering course and developed symptoms of an acute abdomen. An elevated calcium level was noted and because the diagnosis of adrenal insufficiency rather than a surgical abdomen then was considered, a pancreatic amylase was measured and found to be elevated. She was given an ACTH-stimulation test and her baseline and stimulated cortisol concentrations were 55 nmol/l. She was placed on hydrocortisone therapy and her symptoms resolved. She died while still on glucocorticoid therapy so recovery of her HPA axis could not be studied.

After the results of this infant’s testing were known, a clinical decision was made to test all infants with Cortrosyn® 1 week off therapy. Two of the ten infants

\[\text{Table 2. Peak EGF value: EGF/Cr (\(\mu\)mol/\(\mu\)mol).}\]

<table>
<thead>
<tr>
<th>Sex</th>
<th>Pretreatment</th>
<th>Peak</th>
<th>Post-therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsive</td>
<td>17 ± 3</td>
<td>150 ± 46(^b)</td>
<td>100 ± 21(^d)</td>
</tr>
<tr>
<td>Non-responsive</td>
<td>15 ± 5</td>
<td>75 ± 30(^c)</td>
<td>30 ± 11</td>
</tr>
</tbody>
</table>

\(^a\) \(p < 0.005\), responsive versus non-responsive. \(^b\) \(p < 0.001\), peak versus pretherapy. \(^c\) \(p < 0.05\), peak versus pretherapy. \(^d\) \(p < 0.01\), post-therapy versus pretherapy.

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**Fig. 1. Urinary EGF values (mean ± sd) for control (○) and responsive-treated infants (●).** Birth: sample within first 24 h of life; pre: sample before therapy; peak: sample with the highest EGF value; post: sample after therapy completed; \(^*\) \(p < 0.01\) for control versus treated infants; \((\triangle)\) \(p < 0.05\) for treated versus control.
were off dexamethasone therapy but had not been tested at the time of death. Eight of the ten infants treated received a stimulation test. Five had a normal response to the first test. Three infants did not increase their cortisol values to greater than 138 nmol/l on the first test but all infants had values greater than 138 by week 2 off therapy (250, 280, 330 nmol/l, respectively). Because we had no data upon which to decide therapy for a "failure" to increase cortisol values, we chose to observe clinically the infants between the two tests and suggested that stress doses of glucocorticoid hormones be used if the infant developed a significant stress before retesting. None of the infants developed problems between the tests and all released cortisol greater than 280 nmol/l above baseline (690, 540, 599).

Discussion

This is the first report to suggest that dexamethasone increases urinary EGF concentrations in the preterm infant. There was no change in EGF values when dexamethasone was used for three to five doses. The EGF values increased significantly in all infants treated for greater than 1 week. The increase was often to a concentration higher than the values seen in the comparison group that recovered spontaneously from ventilatory support. Also, peak values were higher in infants that tapered successfully off therapy compared to values from the non-responsive group.

It is possible that the infants were treated just as they were entering the time of endogenous increase in EGF values. There was no conclusive way to address this issue in this population in that all infants who met the clinical criteria were treated with dexamethasone. Results from a group of 28 infants who spontaneously increased their urinary concentrations would suggest that endogenous values increase in a stepwise fashion rather than a dramatic increase over 1–2 weeks (15).

Further evidence that the change in EGF values was due to exposure to dexamethasone was the finding that all infants increased their EGF values after 1 week of therapy. The pretherapy values available in some of the treated infants for several weeks prior to therapy were not different from birth values. Then, associated with 1 week of therapy, a significant increase in EGF excretion occurred. This time period has been noted to be sufficient for induction of the EGF receptor by dexamethasone (6). Therefore, if there was a direct effect of dexamethasone on EGF production in the kidney, 1 week of therapy should be sufficient time for the effect to be measurable.

We suggested in our longitudinal study that a rise in EGF values may be necessary for recovery from ventilatory support because of its role in healing (15). Results of the present study extend those observations. Successful recovery from ventilatory support correlated first with an acute and then a sustained increase from pretherapy EGF values. The comparison group and the treated group were comparable for initial ventilatory settings, sex and gestational age. This type of matching suggested that they were clinically similar to each other for those variables that we know are important to the outcome of ventilatory disease in the preterm infant. Within these boundaries, the comparison group was tapering from support at the postnatal age that the treated infants were not. All treated infants had lower pretherapy EGF values than the values for the comparison group of infants who had recovered from ventilatory support at the same postnatal ages without dexamethasone. This difference occurred in the setting of similar EGF values at the time of delivery and a spontaneous increase in EGF values in the comparison group. Recovery from ventilatory support in the treated groups was associated with a rise in EGF concentrations into the same range as values from the comparison group. Further, a return of EGF values to pretherapy values was associated with continued ventilator dependence.

The only clinical finding at the time of therapy that was significantly different between the treatment groups at the beginning of the therapy was the age at which therapy was initiated. Infants that recovered successfully from ventilatory support were younger at the time therapy began compared to those infants that remained ventilator dependent. The high mortality rate for the non-responsive group is consistent with outcome for infants who are not treated with dexamethasone as well as those who do not respond clinically to this type of therapy.

We suggest that this finding is consistent with a period of sensitivity to dexamethasone therapy for
recovery from lung disease. The association of recovery with a significant increase in EGF excretion may reflect a generalized effect of dexamethasone on clinical recovery. An alternative explanation is that the dexamethasone effect on the kidney resulting in increased urinary EGF values may reflect a generalized effect of dexamethasone on EGF production. Because of the role EGF has in lung development (18) and the known role of EGF in healing (19), we speculate that our results are consistent with a role for EGF in dexamethasone-induced lung recovery.

The description of four (of nine tested) infants with a modest release of cortisol with ACTH stimulation is consistent with concerns raised in similarly treated infants (20). The clinical relevance of this finding is unclear, particularly in the context of the recently described gestational age-dependent differences in the ACTH test (21).

In summary, improvement in ventilatory support associated with use of dexamethasone for chronic lung disease correlated with a significant increase in EGF values compared to pretherapy concentrations.

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