Effects of Prenatal Fenoterol, Phenobarbitone and Dexamethasone Administration on the Total Phospholipid Content of Amniotic Fluid

K. D. GUNSTON, D. A. DAVEY

SUMMARY

The effect of prenatally administered phenobarbitone, fenoterol (a β-sympathomimetic drug) and dexamethasone on fetal pulmonary maturity, as measured by the total phospholipid (TPL) content of amniotic fluid, was assessed. Compared with control values, there was a significantly greater rise after fenoterol (P<0.01) and dexamethasone (P<0.01), but not after phenobarbitone administration. The ability of dexamethasone to convert the TPL value to mature levels (≥2.0 μg/ml) was significantly greater than that of fenoterol (P<0.05).


A prenatally administered agent which would accelerate fetal pulmonary maturity without harming mother or fetus would be a great advantage in the management of high-risk pregnancies requiring delivery prior to fetal lung maturity.

Corticosteroids have been used for this purpose1,2 and it is felt that the risk of death from hyaline membrane disease (HMD) in infants delivered without adequate amounts of lung surfactant at any gestational age outweighs any documented hazard from corticosteroids given to the pregnant patient before delivery.3

It has also been suggested that other drugs such as β-sympathomimetic substances used to inhibit premature labour may have a protective effect on the fetus.4,5 There is also a possibility that intra-uterine stress consequent on premature rupture of the membranes or premature labour might induce fetal lung maturity and the use of corticosteroids in such cases may do little to improve the response of the fetus.6,7

The present research was performed to compare the effect of either no treatment, or the use of fenoterol (a β-sympathomimetic agent), phenobarbitone or dexamethasone given to women who required premature delivery because of complications of pregnancy such as severe proteinuric hypertension or idiopathic fetal growth retardation. The total phospholipid (TPL) concentration in the amniotic fluid was used as an index of fetal lung maturity. The amniotic fluid was obtained by amniocentesis before treatment and 96 hours later.

PATIENTS AND METHODS

All patients in premature labour and/or with premature rupture of the membranes were excluded, in view of the suggestion that labour and premature rupture of the membranes may in themselves accelerate pulmonary maturity.

Pregnant women, who gave their informed consent, were selected according to the following criteria: (a) the presence of a severe complication of pregnancy requiring urgent termination of the pregnancy, associated with the absence of lung maturity and hence a substantial risk of the infant's developing HMD; (b) gestational age over 28 weeks and under 35 weeks; (c) the absence of any maternal contraindication to any of the drugs used, e.g. diabetes and corticosteroids, porphyria and barbiturates, cardiac disease and β-sympathomimetic drugs.

Patients were randomly allocated to 1 of the following 4 groups: group I — no medication; group II — fenoterol (a β-sympathomimetic agent) 10 mg orally every 6 hours for 12 doses; group III — phenobarbitone 60 mg orally every 6 hours for 12 doses; group IV — dexamethasone 12 mg by intramuscular injection daily for 2 days. Repeat amniocentesis was performed 96 hours after the initial amniocentesis to assess the effect, if any, of the medication on lung maturity.

Extraction of phospholipids from amniotic fluid and measurement of total phospholipid (TPL) phosphorus was performed as described by Bayer et al.8 This method was chosen because it is simple, cheap and reproducible.

RESULTS

All patients were observed carefully for the duration of the study and no complications occurred as a result of either the medication or the amniocenteses.

The pre- and post-treatment TPL values in the 4 groups are shown in Tables I and II.

The mean rise in TPL values of the 3 treatment groups was compared with the mean value of the control group after logarithmic transformation. Logarithmic transformation was done before applying the t test because of a significant difference between the variances. The results were as follows: (i) the mean rise in the fenoterol group was significantly greater than the mean rise in values of the controls (t = 2.87; P<0.01); (ii) the mean rise in the dexamethasone group was significantly greater than the mean rise in the controls (t = 3.40; P<0.01); and (iii) the mean rise in the phenobarbitone group was
TABLE I. TPL VALUES ($\mu$g/ml) IN 4 GROUPS BEFORE AND AFTER TREATMENT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>0.85</td>
<td>1.04</td>
<td>1.09</td>
<td>1.42</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.57</td>
<td>0.85</td>
<td>1.09</td>
<td>2.42</td>
</tr>
<tr>
<td>Controls</td>
<td>1.14</td>
<td>1.14</td>
<td>0.50</td>
<td>0.85</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>1.90</td>
<td>1.04</td>
<td>1.04</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

TABLE II. COMPARISON OF TPL VALUES BEFORE AND AFTER TREATMENT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pretreatment</th>
<th>Post-treatment</th>
<th>Paired</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Controls</td>
<td>0.882</td>
<td>0.349</td>
<td>1.167</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>0.869</td>
<td>0.259</td>
<td>1.504</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>0.788</td>
<td>0.260</td>
<td>1.083</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1.327</td>
<td>0.391</td>
<td>2.277</td>
</tr>
</tbody>
</table>

The ability of the various drugs to cause a rise in TPL values to mature levels is shown in Table III. Using the exact test for fourfold tables, it was found that with dexamethasone the increase in the TPL to mature levels was significantly greater than that found in controls, and with fenoterol and phenobarbitone ($P = 0.02$, $P = 0.02$ and $P = 0.05$ respectively. These are exact probabilities as derived from *Scientific Tables*.

TABLE III. ABILITY OF DRUGS TO EFFECT MATURE TPL VALUES

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Number with mature TPL levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>18</td>
<td>10</td>
</tr>
</tbody>
</table>

DISCUSSION

The administration of dexamethasone and fenoterol prenatally to the pregnant patient was associated with a significant rise in the surfactant content of amniotic fluid. Preterm labour and premature rupture of the membranes may in themselves accelerate pulmonary maturity. Because
of the difficulty in the interpretation of changes in the surfactant content of amniotic fluid in these two conditions, it was decided to exclude all such patients.

We suggest that the administration of fenoterol or dexamethasone to patients requiring urgent delivery in whom the fetus is believed to be at substantial risk of developing HMD is beneficial. Phenobarbitone, although an inducer of enzyme systems, had no significant effect on the surfactant content of amniotic fluid. This study suggests that fenoterol and dexamethasone are effective in accelerating pulmonary maturity and that they have a place in the prevention of HMD.

REFERENCES

Effect of the Duration of Dexamethasone Treatment on the Total Phospholipid Content of Amniotic Fluid

K. D. GUNSTON, D. A. DAVEY

SUMMARY

Obstetric patients requiring premature termination of pregnancy with low levels of surfactant in the amniotic fluid were given dexamethasone for 2 or 7 days to assess the effect of the duration of treatment on the total phospholipid content of the amniotic fluid.

A significant rise in lung surfactant occurred in both groups, but dexamethasone administered for 7 days was not more effective than 2 days' administration. It is suggested that it is not the duration of treatment, but the stage of pregnancy or the functional maturity of the fetus at the time of administration of dexamethasone that affects the outcome.


Immaturity is an important cause of neonatal death, many infants dying after developing hyaline membrane disease (HMD). An important factor in the pathogenesis of HMD is a failure of pulmonary aeration associated with a lack of surfactant. Surfactant is secreted by type II alveolar cells, and secretion increases markedly as the last trimester proceeds. There is evidence that the administration of corticosteroids to pregnant animals increases the production of surfactant in the fetal lungs. Avery found that glucocorticoids induced cytodifferentiation of type II alveolar cells, with resultant synthesis of surfactant and its release into the alveolus. Farrell observed that corticosteroids lead to enhanced biosynthesis of the surfactant precursors phosphatidylcholine and phosphatidylglycerol.

Several workers have studied the effect of glucocorticoids in human pregnancy. Liggins and Howie reported that treatment with betamethasone reduced the incidence of HMD in preterm infants. The ratio of lecithin to sphingomyelin in amniotic fluid (L/S ratio) has been used as an index of surfactant activity. There is agreement that a variety of corticosteroids can increase the L/S ratio to mature levels, but the increase is variable and the values that are associated with normal lung function in the neonate are not always reached. There is some uncertainty about the optimum duration of corticosteroid therapy. There is also some doubt as to the clinical value of such treatment.

This study was designed to assess the effect of the duration of dexamethasone treatment on the development of surfactant activity in the amniotic fluid. Women with premature rupture of the membranes or who were in premature labour were excluded from the study, as these factors may in themselves result in a rise in surfactant activity.

PATIENTS AND METHODS

Thirty patients in whom delivery was contemplated for obstetric reasons and in whom the fetus was believed to be premature on the basis of insufficient surfactant in the amniotic fluid were given dexamethasone 12 mg by