Dexamethasone for treatment of patients mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus


Background: A study was undertaken to evaluate the efficacy of dexamethasone in patients mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus (RSV-LRTI).

Methods: In a multicentre randomised controlled trial patients were randomised to receive either intravenous dexamethasone (0.15 mg/kg 6 hourly for 48 hours) or placebo. End points were the duration of mechanical ventilation, length of stay (LOS) in the pediatric intensive care unit (PICU) and in hospital, and the duration of supplemental oxygen administration.

Results: Thirty seven patients received dexamethasone and 45 received placebo. There was no significant difference in any of the end points between the two groups. In a post hoc analysis patients were stratified into those with mild gas exchange anomalies (PaO2/FiO2 >200 mm Hg and/or mean airway pressure ≤ 10 cm H2O, bronchiolitis group) and those with severe gas exchange anomalies (PaO2/FiO2 ≤200 mm Hg and mean airway pressure >10 cm H2O, pneumonia group). In the 39 patients with bronchiolitis the duration of mechanical ventilation was 4.3 days shorter in the dexamethasone group than in the placebo group (4.9 ± 9.2 days, 95% CI -7.8 to -0.8, p=0.02) and the duration of supplemental oxygen was 3.6 days shorter (7.7 ± 11.3 days, 95% CI -8.0 to -0.1, p=0.048). No differences in end points were found in the pneumonia group.

Conclusions: Dexamethasone had no beneficial effect in patients mechanically ventilated for RSV-LRTI but was found to have a beneficial effect in patients with bronchiolitis.
of viral shedding, RSV immunofluorescence assay of nasopharyngeal aspirate was repeated on days 2, 3, 7, 10 and 14 while the patient was an inpatient. If two consecutive assays were negative the viral shedding was considered to be negative.

Statistical analysis
The previously found difference of 1.5 days in mechanical ventilation was considered to be clinically relevant; in order for this difference to be detected, 60 patients (30 in each arm) would be needed ($\alpha=0.05$, $\beta=80\%$).

Statistical analysis was performed with SPSS for Windows, version 10.1 (SPSS Inc). The Student’s $t$ test was used to compare group means for normally distributed data; otherwise the Mann-Whitney U test was applied. Proportions were compared by the $\chi^2$ test. A two sided p value of $<0.05$ was considered statistically significant. Data were analysed according to the intention to treat principle. Data in the tables are given as mean (SE) unless otherwise stated.

RESULTS
Eligible patients
From December 1997 to March 2001 155 patients met the inclusion criteria and were eligible for enrolment. Seventy patients were not randomised for reasons shown in fig 1. Of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients on admission in the PICU according to treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexamethasone (n=37)</td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
</tr>
<tr>
<td>Age (weeks )</td>
<td>5.9 (0.9)</td>
</tr>
<tr>
<td>Risk group</td>
<td>12</td>
</tr>
<tr>
<td>Premature*</td>
<td>10</td>
</tr>
<tr>
<td>CLD</td>
<td>1</td>
</tr>
<tr>
<td>CHD</td>
<td>1</td>
</tr>
<tr>
<td>Other†</td>
<td>0</td>
</tr>
<tr>
<td>Family history of asthma‡</td>
<td>9</td>
</tr>
<tr>
<td>Duration of symptoms (days)</td>
<td>3.3 (0.3)</td>
</tr>
<tr>
<td>Apnoea</td>
<td>5</td>
</tr>
<tr>
<td>Wheezing</td>
<td>16</td>
</tr>
<tr>
<td>Admission weight (kg)</td>
<td>4.1 (0.2)</td>
</tr>
<tr>
<td>Median (IQR) PRISM score</td>
<td>9 (7–12)</td>
</tr>
<tr>
<td>SIMV/PC</td>
<td>28</td>
</tr>
<tr>
<td>Median (IQR) PIP [cm H2O]§</td>
<td>24 (20–26)</td>
</tr>
<tr>
<td>Median (IQR) PEEP [cm H2O]§</td>
<td>4 (4–5)</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio [mm Hg]</td>
<td>180 (9)</td>
</tr>
<tr>
<td>Time elapsed between start mechanical ventilation and start trial medication (h)</td>
<td>15 (1.2)</td>
</tr>
</tbody>
</table>

CLD=chronic lung disease; CHD=congenital heart disease; SIMV/PC=synchronised intermittent mandatory ventilation, pressure controlled; PIP=positive inspiratory pressure; PEEP=positive expiratory pressure.

*Prematurity was defined as a gestational duration of less than 36 weeks.
†One patient with cardiomyopathy, one patient with lung hypoplasia.
‡Mother, father or sibling with asthma.
§Only in patients with SIMV/PC ventilation.
the 85 patients who were enrolled, 39 were randomised to receive dexamethasone and 46 to receive placebo. After enrolment three patients were withdrawn, one (dexamethasone group) because she died 4 days after admission due to severe cerebral oedema in combination with refractory seizures existing already before inclusion, and two because their medication vials (one containing dexamethasone and the other placebo) were accidentally interchanged. Eighty two patients therefore completed the trial, 37 of whom received dexamethasone and 45 placebo.

Baseline characteristics
The baseline characteristics of the study participants are shown in table 1. The proportion of males was higher in the dexamethasone group than in the placebo group and the dexamethasone group was significantly younger than the placebo group. There were no other differences in baseline characteristics between the two treatment groups.

Outcome
The mean duration of mechanical ventilation in the dexamethasone group was 1.6 days shorter than in the placebo group; this difference was not statistically significant (7.9 v 9.2 days, 95% CI –7.6 to –0.8 days, p=0.02). The mean LOS in the PICU was 2.4 days shorter in the dexamethasone group than in the placebo group but this difference was not statistically significant (7.9 v 10.3 days, 95% CI –6.8 to 2.0, p=0.28).

When colouring is available for 80 patients during the first 24 hours of admission (in case more blood gas analyses were available the worst PaO2/FiO2 was chosen). These patients were stratified into a bronchiolitis group (mild gas exchange anomalies: PaO2/FiO2 >200 mm Hg and/or mean airway pressure (MAP) on the day of admission, analogous to the criteria described by Tasker et al. Arterial blood gas analysis data were available for 80 patients during the first 24 hours of admission.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dexamethasone (n=37)</th>
<th>Placebo (n=45)</th>
<th>95% CI for difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>6.9 (0.7)</td>
<td>8.5 (0.9)</td>
<td>–3.8 to 0.8</td>
<td>0.19</td>
</tr>
<tr>
<td>LOS in PICU (days)</td>
<td>9.1 (0.9)</td>
<td>9.9 (0.9)</td>
<td>–3.4 to 1.8</td>
<td>0.53</td>
</tr>
<tr>
<td>LOS in hospital (days)</td>
<td>15.9 (1.5)</td>
<td>14.9 (1.2)</td>
<td>–2.8 to 4.7</td>
<td>0.52</td>
</tr>
<tr>
<td>Duration of supplemental oxygen (days)</td>
<td>10.0 (1.2)</td>
<td>10.9 (1.0)</td>
<td>–3.9 to 2.1</td>
<td>0.55</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Dexamethasone</th>
<th>Placebo</th>
<th>95% CI for difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis group††</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>18</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>4.9 (0.5)</td>
<td>9.2 (1.6)</td>
<td>–7.8 to –0.8</td>
<td>0.02</td>
</tr>
<tr>
<td>LOS PICU</td>
<td>7.9 (1.4)</td>
<td>10.3 (1.6)</td>
<td>–6.8 to 2.0</td>
<td>0.28</td>
</tr>
<tr>
<td>LOS hospital</td>
<td>14.9 (2.0)</td>
<td>16.0 (1.9)</td>
<td>–6.7 to 4.5</td>
<td>0.11</td>
</tr>
<tr>
<td>Duration of supplemental oxygen</td>
<td>7.7 (0.9)</td>
<td>11.3 (1.6)</td>
<td>–8.0 to –0.1</td>
<td>0.048</td>
</tr>
<tr>
<td>Pneumonia group†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>19</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>8.9 (1.1)</td>
<td>8.1 (1.0)</td>
<td>–2.2 to 3.6</td>
<td>0.61</td>
</tr>
<tr>
<td>LOS PICU</td>
<td>10.1 (1.1)</td>
<td>9.9 (1.2)</td>
<td>–3.1 to 3.5</td>
<td>0.90</td>
</tr>
<tr>
<td>LOS hospital</td>
<td>16.7 (2.2)</td>
<td>14.1 (1.5)</td>
<td>–2.8 to 8.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Duration of supplemental oxygen</td>
<td>12.1 (1.9)</td>
<td>10.4 (1.0)</td>
<td>–2.7 to 6.1</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Arterial blood gas analysis was available for 37 patients in the dexamethasone group and 43 patients in the placebo group.
†Bronchiolitis group: patients with PaO2/FiO2 >200 mm Hg and/or mean airway pressure ≤10 cm H2O.
‡Pneumonia group: patients with PaO2/FiO2 ≤200 mm Hg and MAP >10 cm H2O.
difference in any of the end points between the dexamethasone and placebo treated patients.

Concomitant treatment
There were no differences in concomitant treatment with antibiotics, bronchodilators or paralysing agents between the two treatment groups (table 4). None of the patients received palivizumab before admission or ribavirin during admission. Three patients received corticosteroids after randomisation; two (one from each treatment group) were started after 8 days with the aim of getting them off the ventilator earlier and one in the dexamethasone group was started on corticosteroids after 2 days because of suspicion of adrenal insufficiency.

Side effects
Mean blood pressure both before the start of trial medication (59 v 58 mm Hg in the dexamethasone and placebo group, respectively, p=0.72) and during the first 5 days of admission (42 mm Hg in both groups, p=0.36) did not differ between the two treatment groups. In one patient (dexamethasone group) malignant hypertension developed 3 days after start of the trial medication which later proved to be caused by a renal vein thrombosis. During the first 5 days of admission glucosuria was found on 7 of the 146 days when urine was checked in the dexamethasone group and on 5 of the 163 days when urine was checked in the placebo group (p=0.56).

During the first 2 weeks of admission at least two RSV immunofluorescence assays were repeated in 58 patients (23 in the dexamethasone group and 35 in the placebo group). In six patients in the dexamethasone group and in nine in the placebo group the test became negative (p=0.60).

DISCUSSION
The results of this trial show that dexamethasone does not lead to a shorter duration of mechanical ventilation in patients with RSV-LRTI. Although dexamethasone shortened the duration of mechanical ventilation by more than 1 day in the whole study cohort, this difference did not reach statistical significance. Our results confirm a very recently published trial that also evaluated the efficacy of dexamethasone in mechanically ventilated patients with RSV-LRTI. However, this trial was primarily designed to evaluate differences in virus quantity and the authors stated that it was underpowered to detect differences of <50% between the two groups.\(^1\)

RSV induced respiratory insufficiency may present with two different patterns. The first pattern, classically referred to as bronchiolitis, is characterised predominantly by obstruction of the airways while the second pattern, classically referred to as pneumonia, is characterised by a predominantly restrictive parenchymal lung disease with alveolar consolidation on the chest radiograph and has many features in common with acute respiratory distress syndrome (ARDS).\(^2\) Tasker et al have shown that it is possible to identify the group with four quadrant alveolar consolidation on the chest radiograph (compatible with RSV pneumonia) by using the alveolar arterial oxygen gradient (AaDO\(_2\)) and MAP during the first 24 hours of admission to the PICU. They found that AaDO\(_2\) of ≥400 mm Hg and MAP of >10 cm H\(_2\)O had a very high positive and negative predictive value for a four quadrant alveolar consolidation. In addition, they found that the LOS of this group in the PICU is much longer than for those with mild gas exchange anomalies on admission and suggested that trials evaluating treatment of mechanically ventilated patients with RSV-LRTI should stratify for these two disease patterns.\(^1\) By combining the results of lung function studies in patients with RSV-LRTI with the results of the study by Tasker et al, Newth concluded that patients with mild gas anomalies may reflect a mainly obstructive pulmonary function pattern (i.e. bronchiolitis) while severe gas exchange anomalies are consistent with a severe restrictive pulmonary function pattern (i.e. pneumonia).\(^12,14\) In addition, Newth showed that the AaDO\(_2\) value of ≥400 mm Hg that was used corresponds to a Pa\(_2\)/Fi\(_2\) ratio of approximately <200 mm Hg which is used to define ARDS.\(^12\) By applying a cut off value of 200 mm Hg for the Pa\(_2\)/Fi\(_2\) ratio and of 10 cm H\(_2\)O for the MAP to differentiate between patients with RSV bronchiolitis and those with pneumonia (who did not fulfil both criteria), we found a marked difference in the efficacy of dexamethasone between these subgroups. Dexamethasone reduced mechanical ventilation by more than 4 days and LOS in the PICU by more than 2 days in the bronchiolitis group. In addition, the LOS in hospital and the duration of supplemental oxygen were reduced by dexamethasone, only the latter end point being statistically significant.

For several reasons our results should be interpreted with caution. Firstly, the efficacy of dexamethasone in patients with RSV bronchiolitis was demonstrated by a post hoc analysis. This only generates the hypothesis that corticosteroids may be beneficial in patients with bronchiolitis and needs to be confirmed in a prospectively conducted randomised trial. Secondly, Tasker et al found an important difference in LOS in the PICU between patients with mild gas exchange anomalies and those with pneumonia (who did not fulfil both criteria), we found a marked difference in the efficacy of dexamethasone between these subgroups. Dexamethasone reduced mechanical ventilation by more than 4 days and LOS in the PICU by more than 2 days in the bronchiolitis group. In addition, the LOS in hospital and the duration of supplemental oxygen were reduced by dexamethasone, only the latter end point being statistically significant.

The efficacy of corticosteroids in patients with RSV-LRTI has been studied for decades with conflicting results.\(^10,16–19\) Although some found a beneficial effect,\(^10,18–20\) most well designed randomised controlled trials did not show that corticosteroids were beneficial.\(^10–19\) Like other workers, in an earlier trial we were unable to show that oral prednisolone was beneficial in patients with mild RSV-LRTI.\(^10,19\) However, prednisolone shortened the duration of mechanical ventilation and the LOS in hospital in a small group of patients on mechanical ventilation. The results reported here support our previous findings that corticosteroids are beneficial in a

### Table 4 Concomitant treatment according to treatment group

<table>
<thead>
<tr>
<th>Antibiotic treatment*</th>
<th>Dexamethasone (n=37)</th>
<th>Placebo (n=46)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started before or on admission</td>
<td>24</td>
<td>32</td>
<td>0.8</td>
</tr>
<tr>
<td>Started &gt;1 day after admission</td>
<td>10</td>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>Bronchodilator therapy during admission</td>
<td>19</td>
<td>27</td>
<td>0.65</td>
</tr>
<tr>
<td>Mean (SE) duration of bronchodilator treatment [days]</td>
<td>5.3 (0.6)</td>
<td>5.3 (0.7)</td>
<td>0.98</td>
</tr>
<tr>
<td>Additional corticosteroid therapy</td>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Paralysing agents during admission</td>
<td>9</td>
<td>15</td>
<td>0.47</td>
</tr>
<tr>
<td>Mean (SE) duration of paralysing agents [days]</td>
<td>3.8 (0.7)</td>
<td>4.5 (0.8)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*Amoxicillin (with or without clavulanic acid) or a macrolide were the most frequently prescribed antibiotics.

92% v 75% in the dexamethasone and placebo groups respectively, p=0.36.

**Note:** The table above is a representation of the concomitant treatment according to treatment group. The data includes the number of patients who started the treatment before or on admission, the number of patients who started the treatment >1 day after admission, the number of patients who received bronchodilator therapy during admission, the mean duration of bronchodilator treatment, the number of patients who received additional corticosteroid therapy, the number of patients who received paralysing agents during admission, and the mean duration of paralysing agents.


Hammer J, Numa A, Newth CJL. Provisional new clinical subgroup of patients and RSV bronchiolitis. Further research is needed to identify more precisely patients in the PICU with RSV-LRTI in whom corticosteroids are potentially beneficial. Since no treatment is available for RSV-LRTI, our findings may indicate a step forward in the search for effective treatment. This may have an important socioeconomic impact since hospital admissions for bronchiolitis have increased substantially over the last decade and it is estimated that, in the USA, more than 100,000 children are admitted annually with RSV-LRTI. 10

In our previous trial we used oral prednisolone in a dose of 1 mg/kg/day for 7 days. Because the beneficial effect of prednisolone was mainly seen in the first 3 days, in the current trial a shorter and higher dose of intravenous corticosteroids was used. On the basis of the dose used in patients with laryngitis subglottica and meningitis, 11 the dose of dexamethasone chosen was 0.6 mg/kg/day (equivalent to 6 mg/kg/day prednisolone). The parenteral route was chosen because mechanically ventilated patients were studied.

The beneficial effects of intravenous dexamethasone outweigh the potential side effects. No significant side effects were found in the present study, which is in accordance with what is known about short courses of steroid treatment. 11

In conclusion, dexamethasone was not found to be beneficial in patients needing mechanical ventilation for RSV-LRTI. However, post hoc subgroup analysis suggested a beneficial effect of dexamethasone in a subgroup of patients with RSV bronchiolitis. Although our findings indicate a significant improvement in the therapeutic possibilities for patients with RSV bronchiolitis who need mechanical ventilation, this observation can only be considered hypothetical and should be tested in a prospective randomised controlled trial.

ACKNOWLEDGEMENTS

We thank the trial pharmacists and medical staff and nurses of all participating centres for their help with preparing the trial medication and including patients and completing the trial respectively, and the Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam for their statistical advice and support.

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