Dexamethasone and Salbutamol in the Treatment of Acute Wheezing in Infants

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ABSTRACT. Thirty-two infants, aged 1 to 12 months, hospitalized with acute wheezing, were studied. They were randomly divided into four treatment groups of eight patients each. The treatments were intramuscular dexamethasone or placebo (double-blind), and salbutamol (oral and inhaled), or none (open), in all four possible combinations. The study was carried out as a randomized block design with eight blocks of four infants each, matched by age and clinical score. Average daily improvements, as reflected by changes in the clinical score and length of hospital stay, was essentially the same for infants treated with placebo, salbutamol alone, and dexamethasone alone. However, combined salbutamol-dexamethasone treatment resulted in more than twice the rate of improvement of the other treatments. The difference was statistically highly significant (P < .01). Furthermore, the response of this combined treatment was observed within 24 hours; none of the ten infants in whom there was no significant improvement within 48 hours and neither of the two patients who developed respiratory failure received the combined salbutamol-dexamethasone treatment. A potentiating effect of corticosteroids on the β-adrenergic responsiveness is a possible explanation for the advantage of this combined treatment in the management of acute wheezing in infancy.

Acute wheezing in infancy is a frequent cause of hospital admissions. Presenting as an acute illness, it is usually accompanied by upper respiratory tract symptoms, and characterized by cough, tachypnea, retractions of the respiratory muscle, and increased mucus production. It is not easy to distinguish between bronchiolitis and asthma in an infant who has acute or recurrent wheezing. The lack of clear-cut diagnostic criteria is also evident from the different terminology used in various medical centers, such as “spastic bronchitis,” “wheezy bronchitis,” and “asthmatic bronchitis,” whereas others prefer “the wheezy baby” or “wheezing-associated respiratory illness” (WARI). It is widely accepted that wheezy bronchitis represents part of the spectrum of asthma, as it has been shown that infants who have more than one wheezing episode will frequently develop the typical picture of asthma in later childhood.

There are conflicting reports regarding the value of corticosteroids or β-adrenergic agents in the treatment of acute bronchiolitis or wheezy bronchitis in infants less than 1 year of age. This study was designed to obtain information as objective as possible on the effect of each of these drugs, both alone and in combination, as well as compared with placebo, on infants admitted to the hospital with an attack of acute wheezing.

MATERIALS AND METHODS

Selection of Patients

The study group included infants aged 1 to 12 months admitted with acute wheezing. The patients studied included those who had wheezing associated with upper respiratory tract infection whose illness had been diagnosed as bronchiolitis (first attack of wheezing, with upper respiratory tract symptoms, without atopic background), asthma (current attacks of wheezing with evidence of atopic background) or WARI (acute wheezing, not fitting into the previous two definitions). Infants were excluded if the cause of wheezing was bronchopneu-
monia, congestive heart failure, foreign body aspiration, cystic fibrosis, or postrespirator chronic lung damage. Informed consent for the study was obtained from the parents, and patients were assigned, on a random basis, to one of the treatment protocols. The protocol for this study was approved by the Helsinki Ethics Committee of the Soroka University Hospital.

Treatment Protocol

All infants were given oral or intravenous (IV) fluids to maintain optimal hydration, and they were given humidified oxygen when cyanosis and/or irritability were present. The treatment protocol is shown in Fig 1. Dexamethasone (4 mg/mL) or normal saline (as placebo) were prepared by the hospital pharmacy in double-blind coded vials. These agents were administered intramuscularly (IM), 0.075 mL/kg, on admission, and then 0.025 mL/kg every eight hours during the next three days (dexamethasone dose: 0.3 mg/kg on admission, and then 0.1 mg/kg every eight hours). In addition, half of the patients receiving each of these treatments randomly assigned, were given salbutamol (Ventolin, Allen and Hanburys Ltd, England) or no additional treatment. Salbutamol was given by two routes simultaneously: (1) inhalations: 0.5 mL (2.5 mg) of salbutamol respiratory solution with 2 mL of water for injection, using a Hadson updraft nebulizer and an electric compressor unit; inhalations were given on admission and subsequently every six hours, and (2) orally: salbutamol syrup, 0.15 mg/kg every eight hours. If no improvement was observed after 48 hours, a “relative therapeutic failure” was registered, and salbutamol was administered (same routes and doses) in those infants who were not given this drug earlier (stage 2). Infants who developed respiratory failure and needed assisted ventilation were considered as a “complete therapeutic failure.” They were transferred to the respiratory intensive care unit, and the study protocol was terminated, breaking the individual code to allow for changes in therapy.

Clinical Evaluation

A clinical scoring system was established, based on the one developed by Bierman and Pierson14 (Table 1). The score included respiratory rate, wheezing, cyanosis, and the use of accessory muscles. The maximum possible score was 12, which indicated severe illness. The clinical score was obtained on admission, three hours after the first IM dose, and each morning (8 AM) until discharge. All scores were performed by three of the investigators (A.T., C.B., and D.Y.), and each patient was evaluated by the same physician during the entire period. A controlled pilot scoring of 25 infants by these physicians showed agreement with no differences greater than one point. For purposes of the study, the rate of improvement was calculated as the average decrease in clinical score per day. Duration of hospitalization was the number of days from admission until discharge.

Further Evaluation

On admission, a complete history was taken and physical examination was performed. Anteroposterior and lateral chest roentgenograms, CBC, serum electrolytes, serum immunoglobulin (Ig)E levels (by Phadebas IgE paper radioimmunosorbent test [PRIST] method), and blood samples for titers of antibodies against respiratory syncytial virus and adenovirus were obtained. Measurements of arte-

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**TABLE 1. Clinical Scoring System**

<table>
<thead>
<tr>
<th>Score</th>
<th>Respiratory Rate (breaths/min)</th>
<th>Wheezing</th>
<th>Cyanosis</th>
<th>Accessory Respiratory Muscle Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;30</td>
<td>None*</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>31-45</td>
<td>Terminal expiration with stethoscope only</td>
<td>Circumoral on crying only</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>46-60</td>
<td>Entire expiration and inspiration with stethoscope only</td>
<td>Circumoral at rest</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>&gt;60</td>
<td>Expiration and inspiration without stethoscope</td>
<td>Generalized cyanosis at rest</td>
<td>++++</td>
</tr>
</tbody>
</table>

* If no wheezing is audible due to minimal air entry, score 3.
Arterial blood gases were obtained on admission, and again three hours after the first IM administration of the drug, and each morning for the next three consecutive days. Additional examinations of arterial blood gases were performed according to the clinical condition of the patient. In each case, values for blood gases were determined ten minutes after the infant was breathing room air, and were examined immediately. Blood pressure was measured on admission and every second day.

Study Design

The study was carried out as a randomized block design, with factorial arrangement of the treatments within each block. The blocks were constructed by taking infants of the same age (<6 months, >6 months) and with a comparable severity of illness. Infants with clinical score of 5 or less were not admitted to the hospital. Those with scores of 12 were admitted directly to the respiratory intensive care unit and, hence, not entered in the study. Those entering the study were classified as mildly (clinical score of 6), moderately (7 to 9), or severely (10 or 11) ill. As mentioned, the measure of improvement was the mean decrease in clinical score per day, for the first seven days of treatment, or until discharge, whichever came first. (It should be emphasized that all patients who were not designated “therapeutic failures” ("relative" or "complete") were discharged before seven days. For the failures, average change in clinical score was calculated to time of treatment failure).

The data were evaluated by analysis of variance and t tests of three independent contrasts: main effects of the two agents and their interaction.

RESULTS

Patients

During a 3-month period (October to December 1980), 32 patients were studied: 20 (62.5%) aged 1 to 6 months (mean 3.3 months) and 12 (37.5%) aged 6 to 11 months (mean 8.8 months). There were 20 (62.5%) boys and 12 (37.5%) girls, with a mean age of 5.4 months. The infants were in eight blocks of four patients each. Four blocks included patients who were moderately ill; the remaining four blocks included severely ill patients. At the time of admission, 12 infants had their condition diagnosed as bronchiolitis, 13 as asthma, and seven as WARI.

Past and Family History

Of the 32 infants ten (29%) had had previous episodes of wheezing, and in 14 (43%) there was positive family history of asthma or allergy. Only six infants (18%) had been breast-fed for 2 months or more.

Laboratory Findings

WBC count ranged between 6,800 to 19,000/μL with 0% to 4% eosinophils in the peripheral blood. Serum IgE was higher than predicted values in 41% of the infants. In two infants significant rise in antibody titers (from less than 1:4 to greater than 1:32 by complement fixation tests) against respiratory syncytial virus and adenovirus, respectively, was found. Mean values of arterial blood Pco2, Pco2, and pH obtained on admission are shown in Table 2 and demonstrate that there were no significant differences between the four treatment groups regarding the initial mean values of Po2, Pco2, and pH. Changes in Po2 and Pco2 during the wheezy episode were not significantly different between the four treatment groups (Fig 2).

Radiographic Findings

Three main features were found: Hyperinflation was found in 26 of the films taken on admission, increased pulmonary markings were seen in 12 cases, and pulmonary subsegmental infiltrates were seen in seven cases. Four films were interpreted as normal by the pediatric radiologist.

The mean rate of improvement of each of the four treatment groups is shown in Fig 3. The average initial clinical score was similar for all treatment groups (about nine points). The rate of improvement of the infants treated by the combination of dexamethasone and salbutamol was more than twice that of any of the other treatment groups. There was no advantage to dexamethasone without salbutamol (1.36 vs 1.35), and there was no advantage to salbutamol without dexamethasone (1.33 vs 1.35). Dexamethasone had a significant effect when

| TABLE 2. Arterial Blood Gas Values Obtained on Admission of Four Treatment Groups of Patients* |
|-----------------|----------------|----------------|----------------|
|                 | Placebo        | Dexamethasone  | Salbutamol     |
| Po2 (torr)      | 68.60 ± 17.20  | 64.10 ± 5.22   | 79.50 ± 14.00  |
| Pco2 (torr)     | 38.00 ± 8.04   | 38.80 ± 6.29   | 37.60 ± 8.40   |
| pH              | 7.32 ± 0.06    | 7.34 ± 0.04    | 7.34 ± 0.06    |
|Intervention     | Placebo Dexamethasone Salbutamol Dexamethasone and Salbutamol |
| Mean            | 68.60 ± 17.20  | 64.10 ± 5.22   | 79.50 ± 14.00  |
| (torr)          | 38.00 ± 8.04   | 38.80 ± 6.29   | 37.60 ± 8.40   |
| Standard        | 7.32 ± 0.06    | 7.34 ± 0.04    | 7.34 ± 0.06    |
| Deviation       | 17.20          | 5.22           | 14.00          |
| Standard        | 8.04           | 6.29           | 8.40           |
| Deviation       | 0.06           | 0.04           | 0.06           |

* Values are means ± SD.
given in combination with salbutamol ($P < .01$).

At the end of stage 1 of the treatment protocol, no clinical improvement was noted in ten (32%) of the infants (relative therapeutic failure). Two additional infants later developed respiratory failure and needed assisted ventilation in the intensive care unit (complete therapeutic failure). As shown in Table 3, none of these 12 failures had been treated by the combination of dexamethasone and salbutamol.

Five infants who were treated with dexamethasone alone were considered as relative therapeutic failures at the end of stage 1 of the treatment. A definite clinical improvement was documented in three of them when salbutamol was later administered (stage 2). Such an improvement was seen in only one of the infants in the placebo group who “failed” during stage 1 and were given salbutamol alone during stage 2. No statistical significance was found in this relatively small group of infants.

One infant developed a remarkable tremor as a side effect of salbutamol. No other side effects or complications of the treatment were documented. All infants were discharged after one to 21 days (mean hospital stay 4.9 days). Average hospital stay of the group given dexamethasone and salbutamol was the shortest (2.5 days) but because of the large variability, no statistical significance was noted.

**DISCUSSION**

The results of this study indicate a possible advantage of the combination of corticosteroids and $\beta$-adrenergic agents in the treatment of acute wheezing episodes in infancy. Although the number of infants studied in each group was relatively small, the rate of improvement in the group given dexamethasone and salbutamol was much greater than in the other treatment groups. This difference was highly significant ($P < .01$).

Some clinicians consider corticosteroids to be important drugs in the management of acute wheezing in infancy.9,16,17 This assumption is based on the hypothesis that their anti-inflammatory action can reduce bronchiolar swelling.16 In fact, one study16 indicated a beneficial effect of corticosteroids in acute bronchiolitis in infants. Several other controlled studies have shown that corticosteroids alone offer little, if any, benefit in the treatment of acute bronchiolitis.6-8

**Fig 2.** Average changes in Pco$_2$ and Po$_2$ in four treatment groups: p, placebo; d, dexamethasone; s, salbutamol; ds, dexamethasone and salbutamol.

**Fig 3.** Average rate of improvement in four treatment groups. Abbreviations are defined in Fig 2 legend.
The clinical impression exists that inhaled β2-adrenergic drugs are often effective in treatment of wheezy infants, but this was not confirmed by objective data. Using a whole-body plethysmograph, a definite improvement in specific airway conductance was found recently in 5/8 infants less than 1 year of age, studied during an acute episode of wheezing before and after inhaled salbutamol.19 There is some evidence that corticosteroid therapy may enhance the effect of β2-adrenergic agonist on cAMP production.20,21 These studies were performed following the description of the β-adrenergic theory of the atopic abnormality in asthma by Szentivanyi.22 This theory delineates the role of the β-adrenergic stimulus in maintaining bronchodilation by means of high levels of cAMP. Corticosteroids exert a facilitating effect on the adrenergic nervous system, and can cause an increase in cAMP levels by decreasing the activity of phosphodiesterase in various tissues.23 Clark and Godfrey24,25 suggest that cortisol stimulation of the production of adenylate-cycase may, in part, explain the apparent potentiation of β2-stimulant responsiveness seen in asthmatic patients treated with steroids. Logsdon et al24 showed in vitro the stimulation of leukocyte adenylate-cycase by hydrocortisone and isoproterenol in leukocytes of asthmatic and non-asthmatic subjects. Recently, various autonomic nervous system abnormalities were described in allergic subjects, including hyporesponsiveness to β-adrenergic stimulation and hyperresponsiveness to cholinergic and α-adrenergic stimuli.25,26 Frazer et al27 found autoantibodies to β2-adrenergic receptors in the serum of three patients with allergic respiratory disease. These abnormalities were found also in “preallergic” subjects (asymptomatic with IgE-sensitized mast cells).25,26 It is possible that β-adrenergic or cholinergic receptors are involved in the process of acute wheezing in infancy. This could be related to the reported relative ineffectiveness of theophylline in young infants with bronchiolitis, as shown in a retrospective study.28

The potentiating effect of corticosteroids on the β-adrenergic responsiveness is a feasible explanation for the advantage of the combination of dexamethasone and salbutamol in the treatment of acute wheezing in infants as shown in our study. Average daily improvement, as shown by changes in clinical score divided by the duration of hospitalization, was more than twice the rate of improvement with steroids alone, β2-adrenergic drug alone, or placebo. Furthermore, the response to this combined regimen was observed within 24 hours; the ten infants in whom there was no significant improvement within 48 hours and the two additional patients who later developed respiratory failure had not been given the combined treatment.

We found no correlation between the response to treatment and demographic or clinical factors or laboratory findings (such as age, sex, atopic background, serum IgE levels, or severity of illness). There were no differences in the course of the disease or response to treatment between infants whose condition was diagnosed as asthma versus bronchiolitis or WARI. There seems to be little value in differentiating between bronchiolitis, asthma, and WARI in young wheezy infants, and so it seems appropriate to use the terminology of Godfrey,1 ie, wheezy baby syndrome.

In conclusion, it is evident from this pilot study on a small number of infants that the combination of dexamethasone and salbutamol was effective and safe in the treatment of infants with acute wheezing. These data justify a more extensive study to corroborate the results before the use of such a combined therapy can routinely be recommended.

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