

## Bronchodilators in Bronchiolitis: Do They Work?

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**B**RONCHODILATORS ARE USED in a number of obstructive respiratory diseases of childhood for the relief of airway smooth muscle contraction (ie, bronchospasm). Although bronchodilators only have approved U.S. Food and Drug Administration labeling for the treatment of asthma and COPD, they are commonly used in bronchiolitis. Infants are born with fully functional airway smooth muscle whose mass relative to airway size is fully developed by 25 weeks gestation.<sup>1</sup> In addition, the neural network is intact and functional  $\beta$ -adrenergic receptors exist in fetal airways by 16 weeks.<sup>2</sup> Neonatal  $\beta$ -adrenergic receptors are in similar density in the airway smooth muscle as adults and neonatal bronchial tissue responds similarly to both  $\beta_2$ -agonists and cholinergic stimulation as adult bronchial tissue.<sup>2,3</sup> Thus, differences in response to the various bronchodilators between infants, children, and adults will most likely be due to issues involving mechanisms of airway obstruction, dosing, and drug delivery rather than in pharmacologic responsiveness of the smooth muscle.

The use of bronchodilators in the treatment of acute viral bronchiolitis has been controversial. The issue in acute viral bronchiolitis is whether or not the airway obstruction has a significant component of bronchospasm. Acute severe bronchiolitis, generally secondary to respiratory syncytial virus (RSV) and other viruses, induces airway obstruction via inflammation, edema, and mucus plugging.<sup>4</sup> However, bronchospasm may play a role in those infants with a family history of asthma and/or allergy.<sup>5</sup> Systematic reviews indicate a modest short-term improvement in clinical scores but no improvement in hospitalization rates or duration of hospitalization from short-acting inhaled  $\beta_2$ -agonists.<sup>4,5</sup> Some of the studies included infants with recurrent wheezing and family histories of asthma.

Some have advocated aerosolized epinephrine for its  $\alpha$ -agonist effect producing pulmonary vascular constriction thus decreasing airway edema.<sup>5,6</sup> Studies show no benefit of epinephrine in hospitalized infants but a slightly greater benefit in outpatient treatment compared to albuterol.<sup>5,6</sup> In addition, the meta-analysis of epinephrine versus albuterol suggested slightly greater benefit of epinephrine in the non-hospitalized patients.<sup>5</sup> Unfortunately, many of the studies comparing epinephrine either as a single isomer or racemic mixture often used doses of epinephrine that were higher than that of albuterol in terms of  $\beta_2$ -adrenergic potency. This was likely due to the fact that the racemic epinephrine doses were derived from studies of croup where the  $\alpha$ -agonist

effect is the primary pharmacologic effect and the albuterol doses were derived from studies in asthma. Thus, it was unclear whether the slight differences reported in the earlier studies were due to an  $\alpha$ -agonist effect or just greater  $\beta_2$ -agonist dose. A study published after the meta-analysis giving equivalent  $\beta_2$ -agonist doses of each found no difference between epinephrine and albuterol.<sup>7</sup> This study also failed to find a difference in hospitalization rate between the active treatments and normal saline placebo. In addition, a recent study of a more objective computerized quantification of wheezing and crackles in infants with bronchiolitis found no effect of either epinephrine or albuterol in equivalent  $\beta_2$ -agonist doses.<sup>8</sup> More recently, a large trial ( $N = 703$ ) compared 3 consecutive doses of albuterol nebulized every 20 min with a single dose of racemic epinephrine (11.25 mg).<sup>9</sup> The 3 doses of albuterol together provided about one-half the  $\beta_2$ -agonist dose of the racemic epinephrine; however, trials in asthma have shown that frequent low doses of an inhaled short-acting  $\beta_2$ -agonist are often more effective than single large doses.<sup>10</sup> This is important because these authors did not exclude patients with a history of asthma or other chronic lung disease and they found a decreased hospitalization rate in those patients receiving the albuterol.<sup>9</sup>

Ipratropium bromide was included as the only bronchodilator, one bronchodilator arm of the study or combined with albuterol in the studies included in the bronchodilator for bronchiolitis meta-analysis by the Cochrane Library.<sup>4</sup> This is unfortunate in that ipratropium bromide is an anticholinergic that would only relieve bronchospasm due to cholinergic input as opposed to functional antagonism produced by  $\beta_2$ -agonists that relieves bronchospasm induced by any mechanism. Thus, the reviewers combined drugs of different mechanisms that are inappropriate in a meta-analysis. Ipratropium bromide was ineffective in all of the studies in the meta-analysis as well as a more recent trial.<sup>11</sup> As would be expected, combined ipratropium bromide plus albuterol is no more effective than either drug administered alone.<sup>12,13</sup>

Although the use of corticosteroids in bronchiolitis is shrouded in its own controversies and disappointing outcomes,<sup>14</sup> there has been interest in combination therapy with the  $\beta_2$ -agonists.<sup>15,16</sup> An initial study of 69 children found no difference in improvement in clinical scores in the first 2 h and at 24 h for combination therapy with dexamethasone and either L-epinephrine or albuterol, but did report lower respiratory distress scores in those patients receiving

dexamethasone than placebo.<sup>15</sup> A recent large trial, ~200 patients per group, reported lower respiratory distress scores in the first 60 min with epinephrine plus dexamethasone and epinephrine plus placebo versus placebo but no difference in hospitalization at that time.<sup>16</sup> At day 22, there was a significant difference in hospitalization rate (primary outcome) in the combination group compared to placebo group but only if not adjusted for multiple comparisons.

In conclusion, there is no evidence that warrants the routine use of bronchodilators in acute bronchiolitis. Many early studies and some of the larger newer studies that demonstrated benefit from bronchodilators were contaminated with patients that had recurrent wheezing or asthma.<sup>4,9</sup> Epinephrine with its vasoconstrictive activity offers no advantage over selective  $\beta_2$ -agonists.<sup>7,9</sup> Anticholinergics have no beneficial effects in bronchiolitis. The addition of dexamethasone to  $\beta_2$ -agonists does not appear to add anything to either the acute or chronic outcome from bronchiolitis. In a busy emergency department during an RSV season, it may be appropriate to give a single dose of  $\beta_2$ -agonists, particularly in infants with a history of previous wheezing or family history of atopy or asthma but there is no evidence to support its routine use in patients with acute bronchiolitis without these pre-existing conditions. Patients administered a dose should be monitored carefully for response and the drug should not be continued if no response is detected.

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