Should Oral Salbutamol Remain on the WHO Pediatric Model List?

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Salbutamol is a β2-selective adrenoreceptor agonist which has demonstrated bronchodilatory effects and is extensively used in the treatment of reversible obstructive airways disease, particularly asthma.¹

The onset of maximum effect of salbutamol is dependent on the formulation used and the route by which it is administered. While both inhaled and oral administrations of the drug have demonstrated considerable bronchodilatory effects, the inhaled route offers direct delivery to affected tissues and has a quicker onset of action. Inhaled salbutamol is effective in smaller doses than oral salbutamol and causes fewer side effects. For these reasons, over the last 20 years numerous asthma management reports have recommended inhaled salbutamol as the preferred mode of delivery. The “2007 Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma” exclusively discusses inhaled salbutamol for short-term asthma relief and makes no mention of indications for use of the oral form.²

Given the long-standing belief in the superiority of inhaled salbutamol, a literature review of the safety and effectiveness of oral salbutamol was undertaken with the intent of petitioning for its removal from the WHO Essential Medicines Pediatric List.

The Pubmed searches were:
oral salbutamol OR salbutamol and asthma Limits: Humans, English, All Child: 0-18 years 1721
salbutamol or salbutamol and asthma Limits: Humans, English, All Child: 0-18 years 2139
salbutamol or salbutamol and asthma and oral and inhal* or aerosol or nebulizer Limits: Humans, Randomized Controlled Trial, English 1184
oral salbutamol or salbutamol and asthma Limits: Humans, Clinical Trial, Meta-Analysis, randomized Controlled Trial, Review, English, All Child: 0-18 years 1032
beta 2 agonist and asthma and administration Limits: Humans, Meta-Analysis, Randomized Controlled Trial, Review, English 545
beta 2 agonist and safety and asthma and administration Limits: Humans, Meta-Analysis, Randomized Controlled Trial, Review, English 79
"salbutamol/administration and dosage"[MeSH Major Topic] 1238
This investigation found that oral salbutamol is an effective bronchodilator and also revealed that it in spite of the repeated recommendations in favor of the inhaled form, oral salbutamol continues to be prescribed in certain American settings.\(^3\)

A study performed by Lahdensuo and Alanko and published in 1976 found oral salbutamol and a combination therapy of oral and inhaled salbutamol to be more effective than inhaled salbutamol alone at increasing effort-dependent peak expiratory flow rate (PEFR).\(^4\)
In another 1976 study, Larsson and Svedmyr found oral salbutamol to have a similar effect as inhaled salbutamol on forced expiratory volume in one second (FEV1), though much higher doses of the oral form were needed to achieve this effect and resulted in tremors and increases in heart rate not seen in the inhaled form.\(^5\)

Grimwood et. al. found in a 1981 study that improvements in PEFR from inhaled salbutamol were greater than those achieved by the oral medication, with the bronchodilatory effects of the oral form lasting significantly longer.\(^6\) Doses were oral 4 mg salbutamol, nebulizer 4 mg, rotahaler 0.4 mg.
Mean (±SEM) percentage improvement in peak expiratory flow rate (PEFR) with time in 17 severely asthmatic children given three forms of salbutamol.

Mean peak expiratory flow rate expressed as percentage of that expected and as percentage improvement over baseline values in 17 severely asthmatic children given salbutamol by mouth, Rotahaler, and nebuliser

<table>
<thead>
<tr>
<th>Time after administration</th>
<th>15 min</th>
<th>45 min</th>
<th>90 min</th>
<th>4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of expected value</td>
<td>% improvement over baseline values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablet</td>
<td>58</td>
<td>87</td>
<td>91</td>
<td>97</td>
</tr>
<tr>
<td>Rotahaler</td>
<td>60</td>
<td>98</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td>Nebuliser</td>
<td>59</td>
<td>101</td>
<td>107</td>
<td>107</td>
</tr>
<tr>
<td>Tablet</td>
<td>60</td>
<td>67</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Rotahaler</td>
<td>73</td>
<td>78</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Nebuliser</td>
<td>98</td>
<td>110</td>
<td>111</td>
<td>111</td>
</tr>
</tbody>
</table>
A study by Louridas et. al, published in 1983, found inhaled salbutamol to be more effective than oral salbutamol in increasing FEV1 but also showed the combination of oral and inhaled salbutamol to be somewhat more effective than either route alone.\(^7\)

Lee found that inhaled adrenergic agonist had greater bronchodilator effect with fewer side effects than oral doses. The combination had slightly enhanced effect with the same degree of side effects as the oral doses alone.\(^9\).

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**Fig. 1.** Mean changes in FEV\(_1\) expressed as percent change of the baseline value in the four regimens. I + O = combined regimen; I = inhalation; O = oral; P = placebo.

**Fig. 2.** Mean changes in FVC expressed as percent change of the baseline value in the four regimens. I + O = combined regimen; I = inhalation; O = oral; P = placebo.
Thus this review re-affirms the present view of the superiority of inhaled vs oral beta agonists for efficacy for treating asthma. Whether it has superior effectiveness in treating patients in unselected populations with asthma under usual use conditions has not been studied.

A PubMed search for effectiveness of inhaled beta agonists (asthma + human + English + effectiveness + beta adrenergic agonists + inhalers, May 27, 2008) yielded no papers. A search of the above deleting beta adrenergic agonists yielded a review. The studies reviewed were of steroid or combination inhalers in asthma. The findings were that many subjects failed to comply with the recommended technique for using the inhalers with consequences ranging from none to critical errors.
Melani presented a similar table for powder inhalers. Proper use of inhalers requires detailed attention to technique. None of the studies reviewed here addressed the question of effectiveness of adrenergic agonist inhalers in actual use.

In recent years, there has been concern about chlorofluorocarbon (CFC) propellants in inhalers. This gas damages the earth's ozone layer. CFC-free inhalers have been mandated for the United States. An article in the NY Times noted that these are much more expensive than the CFC-containing inhalers. In addition, it noted full compliance with the method of use is easier with the CFC-containing inhalers than with those that are CFC-free.

The results of these studies suggest that in spite of the increased systemic effects seen with oral salbutamol, it affords clinically significant bronchodilation and should be considered a treatment option in cases where patients are unable to coordinate use of an inhaler. Furthermore, the continued prescription of oral salbutamol in East and Central Harlem, New York, discussed by Bonner et al, raises questions about situations where the oral form may prove to be a more viable treatment option than the inhaled form. While the authors of this study suggested that the high rate of oral salbutamol prescription in this inner-city setting could be attributed to “sub-optimal medical management,” further investigation into the healthcare providers’ rational behind prescribing salbutamol could provide insight into circumstances in which the oral form is indeed a more effective intervention. One pediatrician who practices in Harlem made the point in a personal discussion (with MMR) that it is nearly or actually impossible to

<table>
<thead>
<tr>
<th>Phase of recommended inhalation technique</th>
<th>Percentage of non-compliance with the recommended procedure</th>
<th>Clinical consequence of non-compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removing the cap from the mouthpiece</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Shaking the inhaler immediately before use*</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Emptying or almost emptying the lungs before activating the spray</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Placing the mouthpiece in the mouth, closing lips around it and avoiding any obstruction by the tongue, or placing the mouthpiece approximately 3-4 cm in front of the mouth, which is kept wide open</td>
<td>+ from - to X</td>
<td>-</td>
</tr>
<tr>
<td>Keeping the spray with the longest part pointing upwards during delivery</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Activating the inhaler once only with a single inhalation *</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Activating the inhaler during the first half of inhalation</td>
<td>+++</td>
<td>from -- to X</td>
</tr>
<tr>
<td>Slowly inhaling while activating the inhaler</td>
<td>+++</td>
<td>--</td>
</tr>
<tr>
<td>Continuing to fill the lungs completely without stopping after delivery of the dose</td>
<td>+++</td>
<td>--</td>
</tr>
<tr>
<td>Holding breath for at least 8-10 seconds or for as long as possible when inhalation is complete</td>
<td>+++</td>
<td>--</td>
</tr>
</tbody>
</table>

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* If the spray had not been used in the previous 3-4 days, it is advisable to deliver 1-2 puffs without inhaling; Noncompliance reported occasionally = +; Noncompliance reported quite frequently (up to 25% of the total) = ++; Noncompliance reported frequently (up to and more than 50% of the total) = +++; Clinical consequence of this variety of misuse is slight = -; Clinical consequence of this variety of misuse is moderate = --; Critical error, such as to reduce drug lung deposition totally = X
enable a 15 year old mother to use effectively inhaled beta adrenergic agonists for her 2 year old child. Another anecdote was that an adolescent boy refused to use an inhaler since being seen using an inhaler by his friends would mark him as a weakling. The cost of inhaler or spacer devices may be too expensive for some patients or health care systems to afford while they can afford oral tablets.

Healthcare providers may not have the time or resources to support the educational effort to initiate inhalation therapy or the resources to continually re-educate some parents adequately on proper inhalation technique. Under some of these circumstances, the oral form would be the better treatment option than the inhaler used improperly. Before the salbutamol tablets are removed from an Essential Medicines list limiting their availability, there should be, at a minimum, a period of training of health care workers and progressive introduction of inhalers into the communities where tablets are widely used.

There is conflict between what academic physicians recommend and what community physicians prescribe. The community physicians’ practice may be quite appropriate for the specific patients receiving oral beta agonists despite the clinical pharmacological advantages of the inhaled form of the medicine. A proper comparative effectiveness study comparing inhaled vs oral beta agonist in at least one appropriate and representative population of very young children and another of adolescents is needed before oral beta agonists are removed from the Model List. This would determine if the inhalers, despite their demonstrated efficacy, are as effective for this population as oral beta adrenergic agonists. It would help define the place for oral beta agonists, if any, in the therapeutics of childhood asthma.

Until much more is known about extent of usage of the oral form in multiple settings and the reasons why the community physicians are prescribing the oral form rather than the inhaled form, we suggest that both forms remain on the Model List of Essential Medicines for Children in appropriate dosage forms for children of all ages.


Additional References:


