Peer reviewed article

A complementary combination of delivery device and drug formulation for inhalation therapy in preschool children

Karen G. Schüepp[a], *Sunalene Devadason*[b], *Christina Roller*[b], *Johannes H. Wildhaber*[a]

[a] Swiss Paediatric Respiratory Research Group, Division of Respiratory Medicine, University Children's Hospital, Zürich, Switzerland

[b] Perth Medical Aerosol Research Group, UWA School of Paediatrics and Child Health, Princess Margaret Hospital, Perth, WA, Australia.

Summary

The amount of drug delivered from commercially available inhalation devices which reaches the lungs of preschool children is generally low. We therefore studied the efficiency of lung delivery from an optimised combination of delivery device and drug formulation based on individual patient-related factors.

In six three-year-old children we compared the delivery of a radiolabelled budesonide solution with a MMD of 4.2 µm from a conventional nebuliser, with that of a radiolabelled budesonide solution with a MMD of 2.5 µm from a perforated vibrating membrane nebuliser.

Lung deposition of budesonide delivered from the perforated vibrating membrane nebuliser was 36% and 38% and notably higher than from a conventional nebuliser (maximum 8%).

The development of complementary combinations of delivery devices and drug formulations to meet the needs of efficient inhalation therapy in preschool children seems to be a good way of improving the efficacy of inhaled therapy in this age group.

Key words: inhalation therapy; aerosols; childhood asthma; radiolabelled aerosols; nebuliser; pressurised metered-dose inhaler

Introduction

Inhalation therapy is currently the most common method of delivering drugs to children with lung diseases [1]. Asthma is the lung disease most widely treated with aerosols, and inhalation therapy is used in millions of asthmatic children throughout the world [2]. Cystic fibrosis, among other rare lung conditions, is a disease requiring regular aerosol treatment in which early and efficient aerosol therapy is crucial for the long-term prognosis [3]. Aerosols, in addition to their use in treating children with lung disease, may soon play an important role as a therapeutic option in the treatment of systemic diseases [4].

Despite the overall importance of aerosol therapy, surprisingly little is known about the technical and practical aspects of aerosol administration to children in general and to preschool children in particular. Most of the knowledge has so far been transposed from adult studies and may partly apply to older children and adolescents but not to preschool children. The efficiency of aerosol therapy with currently available inhalation devices and drug formulations in preschool children is low [1]. However, early and efficient therapy in preschool children, and hence in early life, is crucial for the long-term prognosis of most lung diseases. This underlines the importance of aerosol research in young children, who form an age group requiring special aerosol delivery devices and techniques.

In this pilot study we set out to assess the effect of an optimised combination of inhalation device and drug formulation on the efficiency of aerosol delivery to preschool children.

This study was supported by the Zürich Lungenliga.

Methods

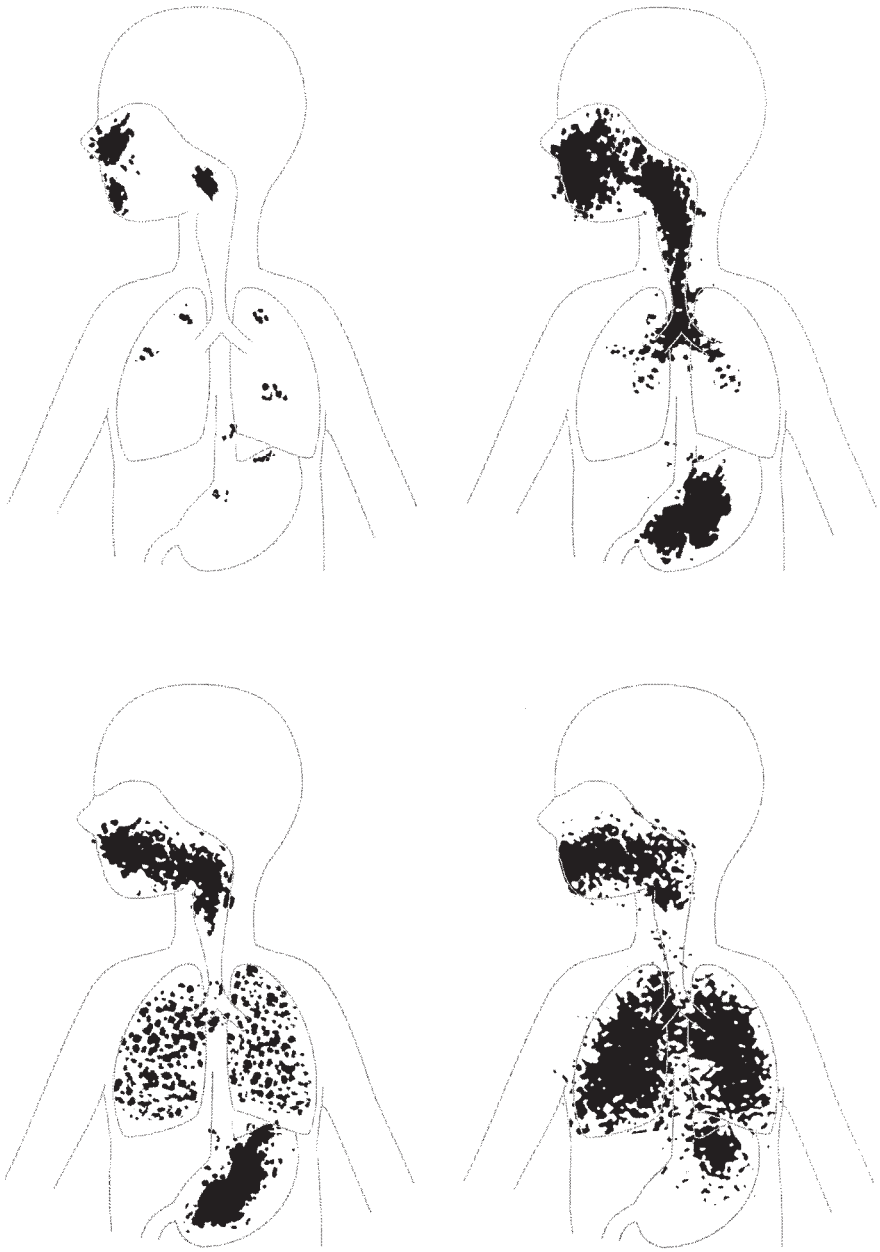
We measured in vivo lung deposition in six asymptomatic, recurrently wheezy children (a: 32 months; b: 36 months; c: 34 months; d: 33 months; e: 38 months and f: 31 months of age respectively). Four children inhaled technetium^{99}-radiolabelled budesonide with a mean mass diameter (MMD) of 4.2 µm and a geometric standard deviation (GSD) of 2 µm from a conventional nebuliser (PARI Boy compressor with PARI LC Plus nebuliser; PARI GmbH, Starnberg Germany), one with a not tightly fitting face mask (a), one crying during inhalation (b) and two children quietly inhaling with a tightly fitting face mask (c and d). Two children quietly inhaled technetium^{99}-radiolabelled budesonide with an MMD of 2.5 µm and a GSD of 1.25 with a tightly fitting face mask from a perforated vibrating membrane nebuliser (e-Flow®, PARI GmbH, Starnberg Germany) (e and f). Lung deposition was assessed with a gamma camera taking anterior and posterior images of the head and upper airways, chest and abdomen, and expressed as a percentage of the nominal dose. The study was approved by the institutional ethics committee (Princess Margaret Hospital for Children, Perth, WA, Australia).

Results

Lung deposition in the four children inhaling from a conventional nebuliser was 0.1% (not tightly fitting face mask, a) 1% (crying, b) and 5% and 8% (quietly inhaling with a tightly fitting face mask, c and d) respectively, whereas in the two children inhaling quietly with a tightly fitting face mask from a perforated vibrating membrane nebuliser (e and f), lung deposition was 36% and 38% respectively (Figure 1a, b, c and d respectively).

Figure 1

Lung deposition in three children inhaling from a conventional nebuliser (top left, child a: not tightly fitting face mask (0.1%); top right, child b: crying during inhalation (1%); bottom left, child c: quietly inhaling with a tightly fitting face mask (8%), and bottom right, child e: lung deposition in a fourth child inhaling quietly with a tightly fitting face mask from a perforated vibrating membrane nebuliser (36%).



Discussion

The treatment of lung diseases in children requires special knowledge of disease presentation in this age group and hence greatly depends on the type and dose of drug selected on the basis of the assumed diagnosis. In addition, there are patient- and device-dependent factors which greatly influence the efficiency of aerosol therapy.

The major patient- or age-dependent factors are cooperation and compliance, together with special characteristics of airway anatomy and breathing patterns. Young children may in the ideal situation only comply with passive inhalation and are only able to inhale through a face mask [5, 6]. Tight sealing of the face mask is crucial in avoiding major drug loss [7]. However, in the majority of cases young children refuse to cooperate at all or, even worse, fight their caregiver's attempt to administer the aerosol [8, 9]. This results in an inadequately fitting face mask, or a screaming child, or total cessation of inhalation therapy, and therewith reduced lung deposition (Figure 1a and 1b). Several previous radiolabelled lung deposition studies have shown that with age lung deposition increases and oropharyngeal deposition decreases [10–12]. In other words, young children have low lung deposition and high oropharyngeal deposition, due to a smaller airway anatomy and characteristic breathing patterns [13]. Due to these factors, the use of smaller drug particles than currently delivered by commercial aerosol delivery devices may be necessary to reach the lungs of small children. The optimal MMD for inhalation therapy in preschool children is probably less than 3 µm [14].

In this pilot study we have shown that in young children lung deposition with a commonly available commercial inhalation device producing an aerosol with an MMD of 4.2 µm is still very low, even in a quietly inhaling child. When using an aerosol with a smaller MMD of 2.5 µm produced by a perforated vibrating membrane nebuliser, lung deposition is shown to be higher. However, further investigations into lung deposition in a larger number of children over a wider age range are needed to verify the findings from this pilot study in a very small number of children.

Our results underline the importance of developing optimum delivery devices and drug formulations adapted specifically for use by preschool children. We conclude that the respirable fraction in preschool children is considerably smaller than that in older children and adults. New developments in inhalation devices and drug formulations, taking into account important device and formulation interactions, will make it possible in further research to determine the optimum particle size for various age groups and various disease groups, and hence will add to our understanding of aerosol therapy in preschool children. In summary, these new developments will have the potential to optimise therapeutic options for all children with lung disease, particularly preschoolers, in the light of their special needs. This will result in improved treatment of lung diseases early in life and very probably decrease the burden of chronic lung diseases in latter life.

Correspondence:
Johannes Wildhaber
Division of Respiratory Medicine
University Children's Hospital
Steinwiesstrasse 75
CH-8032 Zürich
Switzerland
E-Mail: johannes.wildhaber@kispi.unizh.ch

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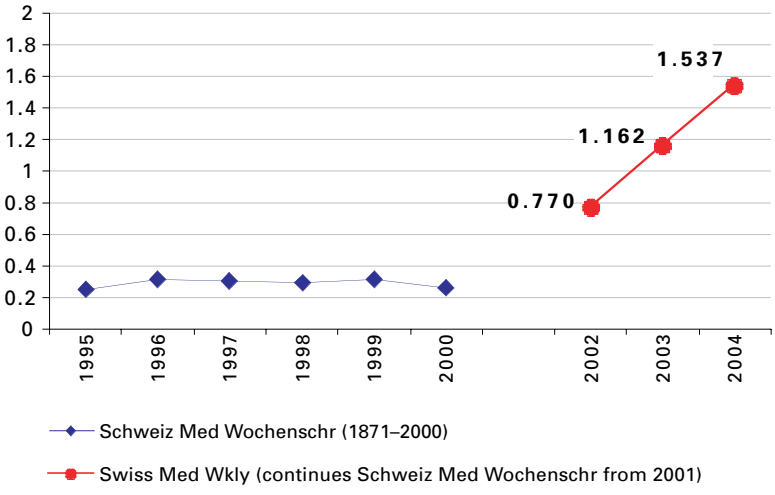

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