Aerosol deposition and clinical performance verified with a spacer device made in Brazil

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Abstract

Objective: to assess the pattern of radioaerosol deposition and the clinical performance of a spacer device designed and manufactured in Brazil.

Methods: qualitative assessment of a patient with cystic fibrosis, and semiquantitative analysis of two healthy volunteers; the assessment of pulmonary deposition of Tc-99m phytate was carried out using the Aerogama Medical oxygen-driven nebulizer system attached to the spacer device and an Orbiter gamma-camera (Siemens) connected to a microcomputer. Next, a measured-dose aerosol container with salbutamol was attached to the spacer device for the treatment of 50 children between 4 months and 13 years of age with acute asthma attacks. Postbronchodilator responses were assessed by clinical score. Up to four consecutive doses of medication was administered, with an interval of 20 minutes. The clinical score was recorded after each dose.

Results: the qualitative assessment revealed a lung silhouette image comparable to that obtained through conventional inhalation scintigraphy, whereas the semiquantitative assessment showed that 7.5% to 8.0% of the inhaled radioaerosol reached both lungs. Statistically significant differences (P<0.001) were observed by comparing admission clinical scores with those verified 20 and 40 minutes after bronchodilator inhalation; conversely, no significance was obtained for scores measured at 60 and 80 minutes.

Conclusions: although an alternative method was used, scintigraphic assessment revealed an expected pattern of pulmonary deposition. Similarly, clinical performance in the treatment of acute asthma attacks presented results comparable to those obtained with other spacer devices.


Introduction

The prescription of inhalation therapy - a universally acclaimed method - for children who suffer from asthma in developing countries, including Brazil, stumbles upon a wide variety of problems such as limited schooling and the high cost of imported spacer devices available in the market.

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As a result, inhalation drugs are not available to a large portion of the population. Also as a consequence, physicians can not use this therapy in patients who receive care through the federal Unified Health System (SUS). Oral administration of drugs is the only alternative for both acute asthma attacks and intercritical phase prophylaxis. An epidemiological survey conducted in the city of Juiz de Fora, state of Minas Gerais (an important socioeconomic and political center in Brazil), showed that only 14.4% of the children with persistent moderate to severe asthma received some kind of prophylactic medication. Nevertheless, the most alarming fact is that only 4.6% of the study population were using inhalation drugs during medical treatment.

The present study describes the process of research and development of Flumax™ (Flumax Equipamentos Médicos, Belo Horizonte, Brazil) - a spacer device manufactured in Brazil. In addition, we describe results concerning deposition of radioaerosol and clinical performance of this device in cases of acute asthma.

Methods

Project development

Disposable plastic cups or bottles2,3 and saline bottles4 have facilitated the assessment of metered-dose aerosols during asthma attacks. However, these homemade spacer devices are part of an "open" system, since they lack a unidirectional valve, whose major function is to prevent the mixture of exhaled air with the medication in the "inhalation chamber". The idea of designing a valved inhalation chamber system made of alternative materials stemmed from these considerations.

One of the authors (JAR) designed a 600-ml prototype with an inhalation chamber built by joining two Mellita™ coffee filter cups. One end was used for the insertion of the metered-dose aerosol, while the other end received a T-shaped PVC fitting, commonly used in plumbing installations. The latter served as a receptacle for the two valves (the inhalation valve was located at the junction of the coffee filter cup with the fitting, and the exhalation valve was at one end of the tee fitting), in addition to serving as connection to the holding chamber, to the nozzle, and to the exhalation valve receptacle. Although the function of the two valves was different, their design was similar (only inverted). There was no statistically significant difference as to the efficiency of this device in comparison to a nebulizer attached to an oxygen tube in 18 patients with acute asthma.

Later, the results obtained during the acute asthma attack were reproduced through the inhalation of beclomethasone in 11 school children with persistent asthma. Those children were observed from 6 to 10 months. During this period, the clinical and functional deficit present before the introduction of the preventive treatment was partially or totally reversed.6

However, the search for a simpler, monobloc device that would allow one of the two valves to be eliminated, with exhalation through two slots on the mouth piece, was materialized as a "second generation" prototype, developed by another author (PAMC). This prototype was built using one-liter soda bottles; the basic structure of the inhalation valve was maintained, consisting of a movable diaphragm screwed onto the plastic bottle cap. This device was equally efficient in seven patients with bronchospasm (7 to 14 years) who presented an average reduction of 55% in the expected peak expiratory flow rate on admission. All patients were rehabilitated within 30 to 45 minutes after receiving conventional doses of salbutamol.7

After development and testing, industrial-scale production of the spacer device was started.

Description

The spacer device is manufactured with inert and atoxic plastic material, highly resistant to impact (virtually unbreakable). The accessories connected to its rear opening are compatible with metered-dose aerosols available in the market, regardless of manufacturer (Figure 1).

To avoid losing or damaging components when handling the spacer device, the pear-shaped body of the inhalation chamber (a feature present in most models) was built in monoblocs. Furthermore, the unidirectional inhalation valve, consisting of three small, interchangeable parts, is deliberately difficult to disassemble.

This valve is housed directly inside the mouth piece (model for children older than 3) or inside the accessory part (similar to a pipe coupling), enabling the connection of the face mask to the holding chamber body (model for children younger than 3). The exhaled air is eliminated through two lateral holes on the mouth piece (maskless model) or through the coupling that fits the face mask to the holding chamber body. The dead space in the face mask model, which is semitransparent, malleable and anatomical, was reduced to a minimum.

The spacer device holds 650 ml and, depending on the model, varies in weight between 55 (nozzle model) and 75 grams (face mask model). All the materials required for the large-scale production of the spacer device are available in Brazil.

Study design

The study was divided into two complementary parts: laboratory-based assessment of a series of three cases, and clinical assessment through a non-controlled clinical trial. These two parts aimed at analyzing the consistency between
scintigraphic findings - deposition of radioisotope - and clinical response, i.e., the effect of the drug employed (salbutamol). It was expected that, similarly to the radioactive substance, salbutamol would reach the lower airways to exert its effect as a bronchodilator.

Qualitative and semiquantitative analysis of radioaerosol deposition

The assessment of pulmonary deposition is one of the essential steps in checking the performance of a spacer device. Since it is impossible to label salbutamol, pulmonary deposition of radioisotope was assessed by gamma radiation detection using Tc-99m phytate as radioaerosol, and replacing the standard technique with conventional pulmonary inhalation scintigraphy. The Aerogama Medical nebulizing system (Porto Alegre, RS, Brazil) and an Orbiter gamma camera (Siemens), connected to a Microdelta PC (Des Plaines, Illinois, USA), were used. The method is similar to that used by Mallol et al. to analyze the pulmonary deposition of this same radioisotope by nebulizers in children with cystic fibrosis.8

The tests were performed on volunteers in two situations: first, the device was tested in a 9-year-old patient with severe cystic fibrosis for qualitative and comparative assessment; the test was performed before pulmonary scintigraphy (inhalation and perfusion). After that, a 2-year-old child and a 20-year-old adult, both healthy, inhaled radioaerosol using a face mask; the radioactive material that reached their lungs was semiquantitatively assessed.

In both cases, the fine particles of Tc-99m phytate-containing aerosol, produced by an oxygen flow of 10 liters/minute, were projected into the conduit connected to the tube during 20 seconds and, afterwards, directed into the spacer device for more than 30 seconds. Inhalation time was deliberately set at 60 seconds. Using a gamma camera, the radiation on the anterior and posterior chest walls was recorded (2 minutes for each of the faces).

Clinical observations

For clinical assessment, a non-controlled assay was carried out. Infants, children, and adolescents with acute asthma were included in the study. The diagnosis of bronchial asthma was based on the information obtained through anamnesis. This information was collected on anamnesis, which emphasized history of recurrent wheezing, evident response to beta 2 agonists in previous attacks and/or family history of asthma or bronchitis.

Location and length of the study

Our study included 50 patients, who were nonrandomly selected among the patients seeking care at one of the pediatric walk-in clinics sponsored by the Belo Horizonte city government between February and August, 1999.

Classification of acute asthma attacks

Asthma symptoms were classified following international guidelines.9 The criteria described in the global initiative for asthma (GINA) classification were recorded (Table 1).
An arbitrary score between 1 and 4 (zero = normal value) was assigned to each criterion. Intermediate values were accepted when the immediately higher and lower scores did not correspond to the clinical status presented by a given patient.

**Inclusion criteria**

Children and adolescents up to 18 years of age suffering from acute asthma with scores between 1 and 3.

**Exclusion criteria**

Use of bronchodilators and/or corticosteroids in the past 12 hours; coexistence of radiological image suggesting bacterial pneumonia; other diseases associated with bronchospasm and extremely severe acute asthma (score 4).

**Therapeutic regimen**

Inhaled salbutamol was used in doses recommended the GINA (10), that is, 2 to 4 applications of 100 mcg every 20 minutes. If necessary, the procedure was repeated up to a maximum of 4 times.

**Assessment of therapeutic response**

The authors were in charge of the admission and follow-up of the first 15 cases in order to identify problems with the operation of the spacer device and eventual clinical repercussions. Since everything happened as expected, the other patients were assessed by an independent group of pediatricians and/or nurses previously submitted to specific training. It is important to emphasize that this group had previous experience with the classification parameters for acute asthma shown in Table 1, and that they had been using beta 2-agonist metered-dose aerosols attached to spacer devices for 3 to 4 years. Therefore, the group was qualified to assess the clinical response obtained with the spacer device under analysis.

This phase of the study began only after the authors confirmed that the group was proceeding correctly as to the administration of inhaled medication and assignment of the score.

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**Table 1 - Classification of acute asthma episode**

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>Mild (Score 1)</th>
<th>Moderate (Score 2)</th>
<th>Severe (Score 3)</th>
<th>Extremely severe (Score 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>able to walk or lie down</td>
<td>able to speak; short cry; difficulty to feed; prefers sitting</td>
<td>present when resting; not able to feed; prefers sitting</td>
<td></td>
</tr>
<tr>
<td>Speech</td>
<td>sentences</td>
<td>phrases</td>
<td>words</td>
<td></td>
</tr>
<tr>
<td>Consciousness</td>
<td>intermittent agitation</td>
<td>usually agitated</td>
<td>usually agitated</td>
<td>drowsy and confused</td>
</tr>
<tr>
<td>Breathing rate#</td>
<td>increased</td>
<td>increased (+)</td>
<td>increased (+++)</td>
<td></td>
</tr>
<tr>
<td>Use of accessory muscles</td>
<td>usually absent</td>
<td>usually present</td>
<td>usually present</td>
<td>thoracic and abdominal balance</td>
</tr>
<tr>
<td>Wheezing</td>
<td>discreet; wheezing at the end of exhalation</td>
<td>wheezing during exhalation</td>
<td>wheezing during inhalation and exhalation</td>
<td>no wheezing, reduced vesicular sounds</td>
</tr>
</tbody>
</table>

# Normal values: <60 irpm, for infants younger than 2 months; <50 irpm, between 2 and 12 months; <40 irpm, between 1 and 5 years, and <30 irpm, between 6 and 8 years; <20-25 irpm, after 9 years.
Statistical aspects
In addition to the amount of Tc-99m phytate that reached the lungs, we calculated the frequency distribution, means and their respective standard deviations for age, and scores on admission (Tzero) and after 20 (T20), 40 (T40), 60 (T60), and 80 (T80) minutes of salbutamol delivery from a metered-dose spacer device. The scores observed 15 minutes after each session of bronchodilator inhalation were compared to the score obtained on admission (Tzero) using the Kruskal-Wallis test. P values of less than 0.05 were considered as statistically significant.

Ethical aspects
Five adult volunteers, including three authors, participated in the standardization of the pulmonary deposition technique by previously submitting themselves to radioaerosol deposition tests. The three tests with radioactive material were conducted on three other volunteers, two of whom were relatives of the authors. After parental consent, the child with cystic fibrosis was submitted to the test prior to scintigraphic examination, following the recommendation of the assistant doctor, as part of left pneumonectomy propaedeutics.

The protocol for the clinical phase was approved by the Ethics Committee of the institution in which the study was conducted. The authors were always available to the patients and to the group in charge of evaluating them, thus ensuring subsequent clinical reassessments.

Results
Qualitative and semiquantitative analysis of pulmonary radioisotope deposition
Figure 2 shows the distribution of radioaerosol in the lungs of children with cystic fibrosis, who inhaled Tc-99m phytate from the mouth piece (image on the left), and the distribution after conventional inhalation scintigraphy (right image), a technique that may be considered as gold standard, in which a similar oxygen flow is employed with an inhalation period four times higher.

The comparison between the images produced with both techniques reveals a similar pulmonary deposition pattern both in proximal airways and in the peripheral area of the right lung. It is important to underscore that scintigraphy showed that 94.5% of the total uptake observed during the exam corresponded to the right lung - in which the deposition obtained with the spacer was concentrated - while the remaining 4.5% corresponded to the left lung.

The semiquantitative assessment (Figure 3) shows a homogenous distribution of radioaerosol (proximally or
Clinical observations

Characteristics of the study population

The distribution according to gender and age, and the clinical status of the 50 children and adolescents who took part in the non-controlled clinical trial are presented in Table 2.

As described in the table, 66.7% of the study population consisted of boys and the average age was 5.5 (±4.3 years). Children with persistent asthma (72%) were predominant over those with intermittent or episodic asthma attacks (28%), suggesting that the studied group presented more complex forms of clinical asthma.

The analysis of the patients’ scores shows evident and progressive improvement of their breathing pattern after one to four salbutamol sessions (Table 2 and Figure 4); most patients (82%) presented a reduction in their scores after three sessions. The fourth and last salbutamol session was necessary for 9 (18%) out of the 50 patients who participated in the study.

Table 2 - General characteristics and evolution of the clinical score (n=50)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (66.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (33.3%)</td>
</tr>
<tr>
<td>Age (average in years ± SD)</td>
<td>5.5±4.3 (4 months to 13 years)</td>
</tr>
<tr>
<td>Previous history of persistent asthma</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 (72.0%)</td>
</tr>
<tr>
<td>No</td>
<td>14 (28.0%)</td>
</tr>
<tr>
<td>No. of salbutamol sessions</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50 (100%)</td>
</tr>
<tr>
<td>2</td>
<td>50 (100%)</td>
</tr>
<tr>
<td>3</td>
<td>39 (78.0%)</td>
</tr>
<tr>
<td>4</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Score (average ± SD)</td>
<td></td>
</tr>
<tr>
<td>Tzero</td>
<td>2.4±0.8</td>
</tr>
<tr>
<td>T20</td>
<td>1.7±0.6</td>
</tr>
<tr>
<td>T40</td>
<td>1.3±0.7</td>
</tr>
<tr>
<td>T60</td>
<td>1.1±0.7</td>
</tr>
<tr>
<td>T80</td>
<td>0.8±0.6</td>
</tr>
</tbody>
</table>

SD = standard deviation

*P values between Tzero and T20, between Tzero and T40, between Tzero and T60, and between Tzero and T80 corresponded to P<0.001, P<0.001, P=0.05, and P=0.76, respectively.

Figure 3 - Semiquantitative assessment of pulmonary deposition. The images show Tc-99m deposition in two healthy volunteers.
The statistical analysis carried using the nonparametric Kruskal-Wallis test revealed significance for the comparison between scores obtained on admission (Tzero) and those observed 15 minutes after each session (p<0.001) for intervals of 20 (T20) and 40 (T40) minutes. On the other hand, the scores obtained for intervals of 60 (T60) and 80 (T80) minutes were not significant (0.05 and 0.76, respectively).

Only one in 50 patients, whose previous history suggested the presence of moderate to severe persistent asthma and poor adherence to prophylactic inhalation corticotherapy, was not responsive to bronchodilation as specified in the protocol. This child was admitted with a score 3, keeping the same respiratory pattern after two salbutamol sessions carried out 40 minutes after admission. The appropriate therapy, including IV corticotherapy, oxygen therapy, and micronebulization with salbutamol was then introduced.

Discussion

Qualitative and semiquantitative analysis of pulmonary radioisotope deposition

Concerning the qualitative analysis of the Tc-99m phytate deposition pattern in children with cystic fibrosis, it is important to emphasize that in the present study radioaerosol was delivered even to distal areas in the right lung - the main target of inhaled drugs (Figure 2). This result is different from that obtained by Mallol et al.,8 who also employed alternative methods.

In the specialized literature, there are few and usually discrepant data on the pulmonary deposition of radioactive substances using metered-dose aerosols (with or without spacer devices) in young children.11 Most of the studies were conducted with older children and adults and, as a consequence, their results cannot be automatically extended to preschool children or infants.11 Pedersen estimates that 4 to 8% of the medication administered through metered-dose aerosols or nebulizers reach the lower airways, whereas Tal et al.12 obtained only 1.97% (±1.4%) by assessing 15 patients whose average age was 21 months. In adults, however, the administration of metered-dose aerosols reached the lower airways in 7 to 14%.13 In the present study, the deposition rate ranged from 7.50% in the 2-year-old child to 8.03% in the 20-year-old individual (according to semiquantitative assessment), suggesting a satisfactory performance (Figure 3).

It is important to consider that radiation uptake is attenuated by thoracic tissues. For instance, in the presence of soft tissues with a thickness of 5 cm, approximately 50% of the radiation is retained in these tissues.14 Therefore, the deposition rate should be higher than that recorded in the gamma camera.

Nonetheless, as with any analysis of case series, the results obtained based on laboratory assessment employing alternative methods are not conclusive, but generate plausible hypotheses that may be tested in other assessments of pulmonary deposition using (technologically) more adequate equipment. Ideally, these assessments should be...
comparative, contrasting the performance of Flumax® with the performance of devices from other manufacturers.

**Clinical observations**

Since the design of the study did not include a control group, the clinical response observed will be compared to that observed by authors who assessed the efficiency of beta 2-agonists administered through nebulizers or spacer devices for the treatment of acute asthma. Differently from the studies on pulmonary deposition in children, there is a great number of studies on the topic, most of which presented favorable and homogenous therapeutic results.

In five of these studies, independently of the therapeutic regimen, of the device used (spacer or micronebulizer), and of the assessment criteria (clinical and/or functional), there was evident improvement in the breathing pattern between 30 and 103 minutes after successive application of these drugs, equally carried out at intervals of 20 minutes intervals, on average. Those findings are similar to the present observations, since most patients (82%) had their score reduced after one to three bronchodilator sessions within 20 to 60 minutes after admission (Table 2 and Figure 4). In addition, the clinical response presented by the patients seems to be the same observed in everyday pediatric practice, even though most patients (72%) in this group suffered from persistent asthma, implying complicated forms of clinical asthma that are usually not responsive to the isolated administration of bronchodilators, requiring the introduction of systemic corticoids, for example. In this study, systemic corticoid was prescribed to only one among 50 patients.

Therefore, the three complementary levels of assessment employed in the present study, namely qualitative assessment of radioaerosol deposition, semiquantitative assessment of radioaerosol deposition, and assessment of the clinical response to salbutamol delivered with the Flumax® spacer device, revealed a coherent behavior, and therefore, indicate the internal validity of the results. However, the design of the clinical component - a non-controlled clinical trial - and the reduced sample size are two important biases, which do not allow us to reach final conclusions on the efficiency of this device, so that the present results should be interpreted with caution. On the other hand, these results offer fundamental information for future research, preferably a study with caution. On the other hand, these results offer fundamental information for future research, preferably a study with independent and "blind" assessments of the response to inhalation bronchodilators administered through Flumax® and a different spacer device.

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**References**

