Lung Deposition of Fenoterol and Flunisolide Delivered Using a Novel Device for Inhaled Medicines*

Comparison of RESPIMAT With Conventional Metered-Dose Inhalers With and Without Spacer Devices

Stephen P. Newman, PhD; Joanne Brown, BSc; Karen P. Steed, MPhil; Sandra J. Reader, PhD; Heinrich Kladders, PhD

**Study objectives:** To compare lung deposition of fenoterol or flunisolide administered from a novel, multidose inhalation device delivering liquid droplets (RESPIMAT; Boehringer Ingelheim Ltd; Bracknell, UK) or from conventional metered-dose inhalers (MDIs) with and without spacers.

**Design:** Two randomized, three-way crossover studies.

**Setting:** Clinical research laboratory.

**Participants:** Healthy, nonsmoking volunteers.

**Interventions:** In one study, radiolabeled aerosols of fenoterol from the RESPIMAT device and from a conventional MDI with or without an Aerochamber spacer (Trudell Medical; London, Ontario Canada). In the second study, radiolabeled aerosols of flunisolide from a RESPIMAT device, from a RESPIMAT device modified by inclusion of a baffle/impactor in the mouthpiece, and from a conventional MDI with an Inhacort spacer (Boehringer Ingelheim; Ingelheim, Germany).

**Measurements and results:** Assessment of the deposition of fenoterol or flunisolide in the lung and oropharynx using gamma scintigraphy. Safety was assessed based on reported adverse effects and spirometry (FEV₁, FVC, and peak expiratory flow rate) to detect any paradoxical bronchoconstriction. The RESPIMAT device delivered significantly more fenoterol to the lungs than either an MDI alone or an MDI with Aerochamber (39.2% vs 11.0% and 9.9% of metered dose, respectively; p<0.01). Oropharyngeal deposition of fenoterol from the new device was lower than that from the MDI (37.1% vs 71.7%, respectively; p<0.01). The RESPIMAT device deposited significantly more flunisolide in the lungs compared with MDI plus spacer (44.6% vs 26.4%, respectively; p<0.01), while resulting in similar oropharyngeal deposition (26.2% vs 31.2%, respectively). Introduction of a baffle into the RESPIMAT system reduced lung deposition of flunisolide to 29.5%, and oropharyngeal deposition to 7.8% (p<0.01).

**Conclusion:** The RESPIMAT device may prove to be an effective alternative to MDIs for the administration of inhaled bronchodilators and corticosteroids. The high lung deposition and low oropharyngeal deposition may lead to improved efficacy and tolerability of inhaled medications, especially corticosteroids.

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**Key words:** flunisolide; fenoterol; gamma scintigraphy; inhaler devices; lung deposition; oropharyngeal deposition

**Abbreviations:** CFC=chlorofluorocarbon; MDI=metered-dose inhaler

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**Currently,** most drugs used in the treatment of asthma and airflow obstruction are given by the inhaled route. This includes bronchodilators such as β₂-agonists and anti-cholinergics, and anti-inflammatory medications such as corticosteroids, cromolyn sodium, and nedocromil sodium. Inhaled medication is preferable to oral medication because the drug is delivered directly to the airways, allowing lower doses to be used, usually a more rapid onset of action, and a reduced incidence of side effects.1,2

The pressurized metered-dose inhaler (MDI) is the
most widely used inhaler device. It has the advantages of being compact, portable, relatively cheap, and easy to use. However, many patients, especially children and the elderly, do not obtain optimal benefit because they fail to use their MDIs effectively.3-5

Most conventional MDIs contain chlorofluorocarbon (CFC) propellants. However, CFCs are thought to contribute to ozone depletion in the atmosphere and from January 1996, the production of CFCs has become severely restricted in line with the Montreal Protocol.6 Therefore, alternative drug delivery systems for inhalation therapy are needed. MDIs with alternative propellants that do not affect atmospheric ozone are being developed,7 and considerable attention has been focused on the development of dry powder inhalers.8

All currently available inhaler devices have advantages and disadvantages, and there is still a clear need for alternative inhaler devices in order to maximize therapeutic benefits and minimize systemic adverse effects of inhaled medication. The RESPIMAT device (Boehringer Ingelheim) (Fig 1) is a novel, hand-held, multidose device that uses mechanical power from a spring rather than volatile gas propellants to release metered doses (15 μL volume) of solutions for inhalation through a sophisticated system of nozzles.9 This generates a slow, gentle release of active substance over >1 s with a high proportion of respirable particles. Because of the novel mechanism of aerosol generation and the qualities of the spray generated by RESPIMAT, the term “soft mist inhaler” has been coined as a generic term to describe the device.

The aims of the two randomized three-way crossover studies in healthy volunteers reported in this article were to examine, using gamma scintigraphy, the in vivo lung deposition of (1) the bronchodilator fenoterol and (2) the corticosteroid flunisolide following single-dose inhalation. Comparisons were made of the total and regional deposition of these drugs delivered by the new device, conventional MDIs, and MDIs with spacer devices. Furthermore, in the flunisolide study, the effect on lung deposition of a modification of the RESPIMAT by the addition of a baffle in the mouthpiece, designed to eliminate large, "nonrespirable" droplets from the spray, was investigated.

**Table 1—Demographics of Study Volunteers**

<table>
<thead>
<tr>
<th></th>
<th>Fenoterol Study</th>
<th>Flunisolide Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Male/female</td>
<td>5/7</td>
<td>6/6</td>
</tr>
<tr>
<td>Age, yr</td>
<td>27.4 (20-39)</td>
<td>27.3 (20-44)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169.8 (151-188)</td>
<td>168.5 (157-188)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.3 (47-98)</td>
<td>69.8 (52-87)</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>106 (92-125)</td>
<td>97 (83-114)</td>
</tr>
</tbody>
</table>

*Data are given as mean (range).

1Weight was recorded for 11 subjects.
Study Design

Both studies were open, randomized, and of a three-way crossover design. The volunteers were each studied on three separate occasions at least 44 h apart. Radiolabeled drug from one of three inhaler devices was inhaled in a randomized order. In the fenoterol study, subjects received a single dose of fenoterol hydrobromide by (1) the RESPIMAT device (Boehringer Ingelheim), (2) MDI, and (3) MDI with Aerochamber. In the flunisolide study, subjects inhaled a single dose of flunisolide by (1) the RESPIMAT device, (2) a modified version of the RESPIMAT with a baffle in the mouthpiece, and (3) MDI with Inhacort spacer device (Boehringer Ingelheim; Ingelheim, Germany). The metered doses of fenoterol and flunisolide were 100 μg and 250 μg, respectively. In the RESPIMAT, fenoterol and flunisolide were delivered as aqueous and 96% ethanol formulations, respectively.

Radiolabeling of Inhalers

The RESPIMAT and MDI devices that delivered fenoterol or flunisolide were radiolabeled by the addition of the radionuclide 99mTc using methods as previously described.11-12 These methods were validated in vitro using a high-precision multistage liquid impinger and demonstrated that the radiolabeling procedure did not alter the particle size distribution of either fenoterol or flunisolide in the RESPIMAT or MDI, and confirmed that 99mTc is an accurate marker for the in vitro distribution of fenoterol or flunisolide inhaled from both devices.11,12 Each metered dose delivered 10 MBq 99mTc in addition to the drug substance.

Drug Inhalation

Prior to administration of the radiolabeled aerosol, subjects practiced with a placebo MDI or placebo RESPIMAT until they could perform the correct inhalation technique. Inhalers were fired by the investigator approximately 1 s after the subject began inhaling, except that for the MDI with Aerochamber, the inhaler was fired approximately 1 s before inhalation commenced. Subjects inhaled slowly (targeted rate, 30 L/min) and deeply, and after inhalation, breath was held for 10 s. The subjects then exhaled through a filter in order to trap any aerosol particles in the expired air. During dosing, a cotton wool plug was taped across the nostrils in order to trap any particles inadvertently exhaled through the nose. Aerosol inhalation was performed with the inhaler connected in series with a respiratory inductance plethysmograph (Respirtrace) from which duration of inhalation, inhaled flow rate, inhaled volume, and breath-holding pause could be calculated.

Consistency of dosing is an important feature of any inhaler device.13 In the present studies, to ensure delivery of the correct dosage, both the RESPIMAT and MDI were primed with 10 shots that were fired to waste before use on each study day. A further priming shot was fired to waste immediately before dosing in each volunteer.

Gamma Scintigraphy

Immediately following inhalation of the radiolabeled aerosol, images of the posterior and anterior views of the chest and abdomen, a right lateral view of the oropharynx, the dosing apparatus (including wipings from the outer surface of the RESPIMAT nozzle and surrounding plastic casing, baffle, actuator, spacer, and mouthpiece), the nose plugs, and exhalation filter were recorded using a gamma camera (General Electric Ecmicam), connected to a data processing system (Bartec Micas V).

Radioactive counts from the whole lung, lung zones, oropharynx, esophagus, and stomach were corrected for background radiation, radioactive decay, and for tissue attenuation of gamma rays.14 The geometric mean of anterior and posterior lung counts was calculated. Oropharyngeal deposition was taken as the sum of radioactivity recorded in the mouth, pharynx, esophagus, and stomach. Data were expressed as the percentage of the metered dose deposited at each site. A posterior lung ventilation scan using the radioactive inert gas 81mKr was obtained and used to define the lung edges. The lungs were subdivided into central, intermediate, and peripheral zones as described previously.15 The ratio of peripheral to central lung zone deposition (ie, the lung penetration index) was calculated.

Adverse Events

Any adverse events occurring during the course of the study were recorded. Lung function tests (FEV1, FVC, and peak expiratory flow rate) were performed before and 60 min following dosing using a spirometer (Vitalograph Compact Spirometer; Vitalograph; Buckingham, UK) to detect any bronchoconstriction associated with the study treatments.

Statistical Analysis

Deposition data for inhaler devices were compared using the Wilcoxon matched-pairs signed rank test. A p value of ≤0.05 was considered to be significant.

Results

Subjects

As shown in Table 1, the demographic characteristics of the patients in both studies were similar. A total of 12 subjects (5 male, 7 female), with a mean age of 27.4 years and normal lung function (mean FEV1, 106% predicted), completed the fenoterol study, whereas 12 subjects (6 male, 6 female), with a mean age of 27.3 years and a mean FEV1 of 97% predicted completed the flunisolide study.

The mean parameters of inhalation for the two studies given in Table 2 show that subjects inhaled slowly at a rate between 25 and 35 L/min and had a breath-holding pause of approximately 10 s.

Whole Lung Deposition

Whole lung deposition of fenoterol was significantly greater when delivered by the RESPIMAT (mean, 39.2%; p<0.01) compared with the MDI (mean, 11.0%; p<0.01) and MDI with Aerochamber (mean, 9.9%; p<0.01) as shown in Table 3 and Figure 2 (top, a). There was no significant difference in the mean whole lung deposition of fenoterol between the MDI and MDI with Aerochamber. Similarly, the whole lung deposition of flunisolide delivered by the RESPIMAT device (mean, 44.6%) was significantly greater than that delivered by either the RESPIMAT with baffle (mean, 29.5%; p<0.01) or the MDI with...
spacer (mean, 26.4%; p<0.01) as shown in Table 4 and Figure 2 (bottom, b). However, the difference in mean whole lung deposition of flunisolide between the RESPIMAT with baffle and the MDI with spacer was not significant.

**Regional Lung Deposition**

The RESPIMAT deposited a greater percentage of the fenoterol dose in the central, intermediate, and peripheral lung regions than either the MDI or the MDI with Aerochamber (Table 3). The mean penetration indexes for the three regions lay between 1.3 and 1.5, and this parameter was significantly higher for the MDI with Aerochamber than for the RESPIMAT (p<0.05; Table 3).

Comparison of the regional deposition of flunisolide demonstrated that the RESPIMAT deposited a greater percentage of the dose in the central, intermediate, and peripheral lung regions than either the RESPIMAT with baffle or the MDI with spacer (Table 4). The mean penetration indexes were similar for the RESPIMAT and the RESPIMAT with baffle, but was significantly higher for the RESPIMAT compared with the MDI plus spacer (p<0.05). Although the deposition of flunisolide in the central and intermediate lung zones

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**Table 2—Inhalation Details**

<table>
<thead>
<tr>
<th>Duration of Inhalation, s</th>
<th>Inhaled Volume, L</th>
<th>Inhalation Rate, L/min</th>
<th>Breath-holding Pause, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPIMAT</td>
<td>6.7 (2.5)</td>
<td>2.6 (1.3)</td>
<td>24.8 (10.2)</td>
</tr>
<tr>
<td>MDI</td>
<td>5.8 (1.3)</td>
<td>2.6 (1.2)</td>
<td>27.2 (10.4)</td>
</tr>
<tr>
<td>MDI with Aerochamber</td>
<td>5.9 (2.4)</td>
<td>2.7 (0.8)</td>
<td>30.5 (13.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flunisolide study</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPIMAT</td>
<td>5.4 (3.3)</td>
<td>2.4 (1.7)</td>
<td>29.8 (14.7)</td>
<td>10.1 (1.3)</td>
</tr>
<tr>
<td>RESPIMAT+baffle</td>
<td>6.0 (3.5)</td>
<td>2.4 (1.0)</td>
<td>27.4 (10.4)</td>
<td>9.7 (1.2)</td>
</tr>
<tr>
<td>MDI with spacer</td>
<td>5.4 (4.5)</td>
<td>2.5 (1.2)</td>
<td>35.0 (20.1)</td>
<td>10.6 (1.1)</td>
</tr>
</tbody>
</table>

*Data given as mean (SD).
†Data given for only 11 of the 12 subjects.

**Table 3—Percentage Distribution of Metered Dose of Fenoterol in Lungs, Oropharynx, and Recovered From the Dosing Apparatus and Exhaled Air**

<table>
<thead>
<tr>
<th></th>
<th>RESPIMAT</th>
<th>MDI</th>
<th>MDI with Aerochamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole lung, %</td>
<td>30.2 (12.7)†</td>
<td>11.0 (4.9)</td>
<td>9.9 (3.4)</td>
</tr>
<tr>
<td>Central lung zone, %</td>
<td>11.0 (3.7)†</td>
<td>3.1 (1.1)</td>
<td>2.5 (0.9)</td>
</tr>
<tr>
<td>Intermediate lung zone, %</td>
<td>14.1 (4.9)†</td>
<td>3.7 (1.8)</td>
<td>3.6 (1.2)</td>
</tr>
<tr>
<td>Peripheral lung zone, %</td>
<td>14.1 (4.8)†</td>
<td>4.2 (2.1)</td>
<td>3.8 (1.5)</td>
</tr>
<tr>
<td>Oropharyns, %</td>
<td>37.1 (10.4)†</td>
<td>71.7 (7.4)</td>
<td>3.6 (2.4)</td>
</tr>
<tr>
<td>Dosing apparatus, %†</td>
<td>21.9 (6.1)</td>
<td>16.7 (5.4)</td>
<td>86.2 (5.2)</td>
</tr>
<tr>
<td>Exhaled air, %†</td>
<td>1.9 (1.7)†</td>
<td>0.6 (0.4)**</td>
<td>0.4 (0.3)</td>
</tr>
<tr>
<td>Penetration index</td>
<td>1.3 (0.4)†</td>
<td>1.4 (0.4)</td>
<td>1.5 (0.4)†</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD).
†For RESPIMAT=mouthpiece and wipings; for MDI=actuator; for MDI with Aerochamber=actuator and Aerochamber.
‡Includes exhalation filter and nose plug.
$p<0.01$ vs MDI.
$p<0.01$ vs MDI with spacer.
$p<0.05$ vs MDI.
$p<0.02$ vs MDL.
**$p<0.05$ vs MDI with spacer.
***$p<0.05$ vs RESPIMAT (Wilcoxon signed-rank test).

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![Figure 2](image-url) Whole lung deposition of (top, a) fenoterol and (bottom, b) flunisolide in individual subjects. Solid bar represents mean values.
**Table 4—Percentage Distribution of Flunisolide in Lungs, Oropharynx, and Recovered From the Dosing Apparatus and Exhaled Air**

<table>
<thead>
<tr>
<th></th>
<th>RESPIMAT (Baffle)</th>
<th>RESPIMAT (Spacer)</th>
<th>MDI With Spacer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole lung, %</td>
<td>44.6 (7.9)</td>
<td>29.5 (4.4)</td>
<td>26.4 (6.2)</td>
</tr>
<tr>
<td>Central lung zone, %</td>
<td>10.9 (1.9)</td>
<td>7.0 (1.4)</td>
<td>7.4 (2.0)</td>
</tr>
<tr>
<td>Intermediate lung zone, %</td>
<td>15.8 (2.4)</td>
<td>10.4 (1.6)</td>
<td>9.2 (2.1)</td>
</tr>
<tr>
<td>Peripheral lung zone, %</td>
<td>17.9 (4.2)</td>
<td>12.1 (2.2)*</td>
<td>9.8 (2.6)</td>
</tr>
<tr>
<td>Oropharynx, %</td>
<td>26.2 (6.8)</td>
<td>7.8 (2.5)</td>
<td>31.2 (9.6)</td>
</tr>
<tr>
<td>Dosing apparatus, %</td>
<td>16.7 (4.1)</td>
<td>55.4 (7.3)</td>
<td>42.0 (8.8)</td>
</tr>
<tr>
<td>Exhaled air, %</td>
<td>12.4 (8.3)</td>
<td>7.4 (6.0)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td>Penetration index</td>
<td>1.6 (0.3)</td>
<td>1.8 (0.4)*</td>
<td>1.4 (0.5)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD).
†For RESPIMAT=mouthpiece and wipings; for RESPIMAT (baffle)=baffle, wipings, and mouthpiece; and for MDI with spacer=actuator and spacer.
‡Radioactivity on the exhalation filter and nose plug (data from the nose plug is missing for one subject in the RESPIMAT [baffle] group).
*p<0.01 vs RESPIMAT (baffle).
#p<0.05 vs MDI with spacer.
*#p=0.02 vs MDI with spacer (Wilcoxon signed-rank test).

was similar for the RESPIMAT with baffle and MDI with spacer, the RESPIMAT with baffle deposited a significantly greater percentage of the dose in the peripheral region of the lungs than the MDI with spacer (p<0.05). This was reflected in a significantly higher penetration index for the RESPIMAT with baffle compared with the MDI with spacer (p=0.02) as shown in Table 4.

**Oropharyngeal Deposition**

In the fenoterol study, the mean oropharyngeal deposition was significantly lower for the RESPIMAT compared with the MDI (37.1% vs 71.7%, respectively; p<0.01) (Table 3). However, the use of the Aerocamber with the MDI reduced the mean oropharyngeal deposition of fenoterol to 3.6%, which was significantly lower than that for the RESPIMAT or the MDI alone (p<0.01).

The mean oropharyngeal deposition of flunisolide delivered via the RESPIMAT was 26.2%, which was similar to that for the MDI with spacer (31.2%). However, modification of the RESPIMAT by the addition of a baffle significantly reduced oropharyngeal deposition of flunisolide to a mean of 7.8%, as shown in Table 4.

**Deposition on the Dosing Apparatus**

The mean percentage of the fenoterol dose deposited on the RESPIMAT mouthpiece was significantly greater than that on the MDI actuator (21.9% vs 16.7%, respectively; p<0.05), but was much less than that deposited in the Aerocamber and the MDI actuator to which it was attached (86.2%; p<0.01), as shown in Table 3.

Using the RESPIMAT with baffle, a mean 55.4% of the dose was retained on the apparatus, of which a mean 40.8% was on the baffle. By comparison, only 42.0% of the dose was deposited on the apparatus for MDI with spacer (p<0.01), of which a mean 29.1% was on the spacer (Table 4).

**Lung Deposition as a Percentage of Total Body Deposition**

Lung deposition was recalculated as a percentage of total body deposition (lungs plus oropharynx) to give a measure of the degree of selectivity of deposition to the target site. The RESPIMAT device showed considerable improvement in this parameter for flunisolide (mean 63%) when compared to the MDI with spacer (mean 46%). The introduction of a baffle in the RESPIMAT mouthpiece further increased this figure (mean 79%) largely due to the effect on reducing oropharyngeal deposition since the absolute percent of the dose deposited in the lungs was lower than without the baffle. In the fenoterol study, lung deposition from the RESPIMAT as a percentage of total body deposition was dramatically increased compared with the MDI (mean 51% compared to mean 13%). The figure for MDI plus spacer was 73%, but absolute lung deposition was low compared to the deposition achieved with the RESPIMAT device.

**Radioactivity Recovered From Exhaled Air**

In the fenoterol study, only a small percentage of the metered dose from each device was detected in the exhaled air (ie, on the exhalation filter and nose plugs) as shown in Table 3. However, the mean percentage of the dose in exhaled air for the RESPIMAT device was significantly greater than that for the MDI (p<0.02) and the MDI with Aerocamber (p<0.01).

For the subjects receiving flunisolide via the MDI with spacer, the mean percentage of the dose detected in the exhaled air was very low (0.4%). In comparison, both the RESPIMAT and the RESPIMAT with baffle deposited a significantly greater proportion of the dose in the exhaled air (mean 12.4% and 7.4%, respectively; p<0.01) as shown in Table 4.

**Adverse Events**

There was no evidence in either study of any paradoxical bronchoconstriction in subjects receiving fenot-
erol or flunisolide. This is an important observation since the formulations include either the preservative benzalkonium chloride or ethanolic solutions. FEV₁ values before and after dosing for each of the study regimens are shown in Table 5. Otherwise reported adverse events in these studies were unremarkable and reflected the known effects of fenoterol and flunisolide. One subject in the fenoterol study developed generalized tremor immediately after dosing on two of the study days, accompanied by tachycardia on one occasion. Both events resolved spontaneously.

**DISCUSSION**

To achieve good control of obstructive airway diseases, there must be adequate delivery of inhaled bronchodilator drugs to the lungs. However, because many patients have difficulties using currently available inhaler devices correctly, there have been intense efforts to develop inhaler devices that are easy to use and provide improved lung deposition. Ideally, an inhaler device should be able to deliver a range of drugs, including bronchodilators or corticosteroids, so that patients only have to learn how to handle one type of device. For this reason, two studies that investigated the drug deposition of fenoterol and flunisolide delivered by a novel “soft mist inhaler” device, the RESPIMAT, have been presented together in this article. Gamma scintigraphy is a useful method for obtaining information on in vivo drug deposition from inhaler devices. The technique not only gives a visual picture of where the inhaled drug has been deposited, but also provides accurate quantitative information on the distribution of drug within the lungs and in the oropharynx.

In contrast to the MDI, where drug particles leave the canister at a very high speed and initially are of relatively large particle size (mass median diameter, 15 to 20 μm), the RESPIMAT soft mist inhaler generates a slow, gentle release of particles, a high proportion of which are respirable (<5 μm), and which patients may find easier to inhale in clinical practice. These features of the device suggest that lung deposition may be improved, which has been confirmed by the results of the present studies. The mean whole lung deposition of fenoterol and flunisolide delivered by the RESPIMAT device was similar (39.2% and 44.6% of the metered dose, respectively). Such high values of whole lung deposition have only rarely been reported previously with other aerosol delivery devices. Lung deposition >25% of the metered dose has been reported for the Turbuhaler, an MDI containing a propellant-soluble radiolabel and an MDI plus Nebuhaler spacer. The whole lung deposition of fenoterol delivered by MDI (11.0%) was similar to the lung deposition from MDIs obtained in other studies. Moreover, the mean whole lung deposition of flunisolide from the MDI with Inhacort spacer (26.4%) was similar to that obtained in other studies using MDIs with larger-volume spacer devices, where relatively high lung deposition values were recorded. Dolovich et al have also observed lung deposition from MDIs used with or without an Aerocam averaging about 10% of the dose, with oropharyngeal deposition <10%. Inhalation technique has a critical effect on drug delivery to the lungs, but was carefully controlled in these studies, with inhaled volumes, inhaled flow rates, and breath-holding pauses being similar for all devices tested.

Lung deposition calculated as a percent of total body deposition expresses the “selectivity” of delivery to the intended site from inhalation devices. For devices like the RESPIMAT that can produce a high deposition in the lungs, then the amount of oropharyngeal deposition is automatically limited. As a result, a more selective delivery pattern is generated, with a higher proportion of the dose reaching the required site. Consequently, a smaller dose of drug may be needed to produce the required therapeutic effect when a high lung deposition device such as RESPIMAT is used. The combination of the selective targeting of drug to the lung and the possibility of reduced total doses may lead to improvements in the therapeutic ratio of respiratory medicines.

Large particles or droplets delivered from inhaler devices will be deposited in the oropharynx, possibly contributing to unwanted side effects, but making no contribution to clinical efficacy. The addition of baffles to inhaler devices reduces oropharyngeal deposition, but may also reduce drug delivery to the lungs. Modification of the RESPIMAT by addition of a baffle in the mouthpiece reduced oropharyngeal deposition from 26.2 to 7.8% of the dose, and reduced whole lung deposition from 44.6 to 29.5%, with the overall effect that targeting of delivered...
drug to the lungs was improved by the baffle. This improvement in the selectivity of drug delivery for the RESPIMAT with baffle could result in a reduction in both the local and systemic side effects of high dose inhaled corticosteroids.

The percentage of the dose of flunisolide in the exhaled air was significantly greater for the RESPIMAT and RESPIMAT with baffle than for the MDI with spacer (12.4% and 7.4% vs 0.4%, respectively). This reflects the high proportion of small, rapidly evaporating ethanol droplets in the RESPIMAT flunisolide formulation which, despite a 10-s breath-holding pause, did not deposit by sedimentation in the airways. Most of the radioactivity in the exhaled air was on the exhalation filter, with only a very small proportion being detected on the nose plugs.

It is a possibility that the additives, including ethanol, in aerosol formulations can cause bronchoconstriction in some patients with asthma. The RESPIMAT is a multidose device and the fenoterol solution for inhalation contains the preservative benzalkonium chloride. This additive has been shown to cause bronchospasm in some asthmatic patients. However, in the present studies, no paradoxical bronchoconstriction was noted with either drug formulation in any of the healthy volunteers.

In summary, the results from these studies indicate that the RESPIMAT device may prove to be an effective alternative to MDIs for administration of bronchodilator and anti-inflammatory agents in the therapy of asthma and COPD. Improved lung targeting achieved by the RESPIMAT may permit asthma to be treated with a lower daily dose of drug compared with those given by MDI. In patients requiring treatment with high-dose inhaled corticosteroids, where local and systemic side effects are of major concern, the reduced oropharyngeal deposition with the RESPIMAT (baffle) system may be a particularly useful option. Future research should address the effectiveness, side effects, and acceptability of this delivery system, not only in patients with asthma, but also in those with COPD.

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