Systemic Cardiovascular and Metabolic Effects Associated with the Inhalation of an Increased Dose of Albuterol*

Influence of Mouth Rinsing and Gargling

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We designed this investigation to assess the occurrence of systemic beta adrenergic side effects associated with the inhalation of an increased dose of the beta, receptor agonist albuterol. Since therapeutic aerosols delivered by metered dose inhaler (MDI) are preferentially deposited in the mouth and pharynx, we wished to determine whether mouth rinsing and gargling with water might reduce the magnitude of such side effects by partially removing oral and pharyngeal drug residues. Serum glucose, insulin and potassium concentrations, forced expiratory volume in one second (FEV1), heart rate (HR), and blood pressure (BP) were measured as parameters of beta-adrenergic stimulation. Each of eight nonmedicated mild asthmatic patients was studied on two separate days after an overnight fast. Measurements were obtained twice before and then repeatedly at various times up to three hours after inhalation of ten albuterol doses (total dose approximately 1 mg) delivered by MDI. On either day the patient did, or did not, rinse the mouth and gargle after drug inhalation. Aerosol-administered albuterol significantly increased HR, FEV1, systolic BP and serum concentrations of glucose and insulin and lowered diastolic BP as early as five min after inhalation, indicating early systemic drug absorption. Peak changes in all measured parameters were observed within 30 min after treatment. Mouth rinsing and gargling removed 24 ± 1.1 percent of the total albuterol dose delivered, but did not lower the magnitude or shift the time course of these side effects or bronchodilation. Our data suggest that cardiovascular and metabolic side effects are associated with the inhalation of an increased dose of albuterol and that mouth rinsing and gargling are not effective in reducing the magnitude of these systemic effects.

Beta, selective adrenergic agonists are the bronchodilator agents of choice for the treatment of bronchial asthma.1 For maintenance bronchodilator therapy, delivery of these agents by metered dose inhaler (MDI) is the preferred route of drug administration. For example, metered dose aerosols of the beta, selective agonist albuterol (salbutamol) relieve bronchospasm more effectively, more rapidly, and with fewer side effects than tolerable amounts administered orally.4 However, the maximal dose of aerosolized albuterol which can safely be administered to patients, while at the same time providing an optimal therapeutic effect, remains unclear. Several investigators, delivering up to eight consecutive metered doses of albuterol1,4 and as much as 15 mg of the drug by an intermittent positive pressure device1 to patients with bronchial asthma, have observed a positive relationship between the amount of drug administered and subsequent improvement in the forced expiratory volume in one second (FEV1). A similar dose-response relationship has been noticed when increasing doses of albuterol powder (up to 1,600 µg) were delivered to patients with chronic obstructive lung disease.5 These studies indicate that, in some patients, optimal bronchodilation may not be achieved with conventionally recommended drug regimens. Supporting these experimental observations is the well-known clinical fact that patients with obstructive airways disorders often “overuse” their inhalers, a practice which might subject them to the occurrence of undesirable systemic adrenergic side effects.

Inhaled sympathomimetic compounds exert their bronchodilator action primarily through the portion of active aerosol which is directly deposited in the airways.6 An additional small but significant bronchodilator effect results from oral drug deposits,7,8 probably through absorption across the oral mucosa. Furthermore, it has been suggested that systemic adrenergic side effects might be due to drug deposition in the upper airways.9 Approximately 80 percent of the total drug dose delivered by standard MDIs impacts in the mouth and pharynx.10,11 Therefore, we reasoned that mouth rinsing and gargling, a procedure supposed to lower the incidence of oral candidiasis associated with inhaling aerosolized corticosteroids,12,13 might be effective in decreasing the magnitude of adrenergic side effects by removing oral and oropharyngeal drug residues. Consequently, we designed the present

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investigation to assess the extent to which an increased dose of inhaled aerosolized albuterol might affect certain clinically relevant cardiovascular and metabolic parameters, and to evaluate a potentially beneficial effect of mouth rinsing and gargling after albuterol inhalation on the occurrence or magnitude of such side effects.

METHODS AND MATERIALS

Subjects

Eight non-smoking patients with mild bronchial asthma (one woman, seven men), aged 21 to 30 years (average 26 yrs) volunteered to participate in the study by signing the informed consent approved by the University of Kentucky Institutional Review Board. In all patients, the diagnosis of asthma was corroborated by previously-documented airways hyperresponsiveness to inhaled histamine diphosphate. At the time of study, all participants were symptom-free and had an FEV, of at least 70 percent of the predicted normal value. To minimize any possible influence of previous maintenance bronchodilator therapy on beta adrenoceptor sensitivity, none of the patients used any oral or inhaled sympathomimetic drugs for at least two weeks prior to entering the trial. All patients were well trained in the performance of the necessary spirometric maneuvers.

Protocol

Each patient was studied in the morning of two separate days after an overnight fast. Complete drug wash-out was assured by observing an interval of at least one week between testing days. The protocol on both days was identical except that on either day the patient did, or did not, perform the mouth rinse and gargle maneuver after albuterol aerosol inhalation. The sequence of the two days was alternated between consecutive patients.

Initially, the patient’s lung function was measured by spirometry. If FEV, was not at least 70 percent of the predicted normal value, testing was deferred. Otherwise, the patient was placed in the semi-recumbent position and remained so during the entire study. An indwelling catheter was inserted into an ante-cubital vein to facilitate repeated blood withdrawal, and was kept patent by intermittently flushing it with a 0.9 percent sodium chloride solution containing minimal amounts of heparin sulfate. After a stabilization period of at least 30 min, duplicate control measurements of blood pressure (BP), heart rate (HR) and spirometry were obtained ten min apart, and two control venous blood samples were drawn. The patient then inhaled ten metered doses of aerosolized albuterol delivered from a standard, commercially-available MDI (Ventolin, Glaxo Inc., Research Triangle Park, NC). Individual doses were separated by a one min interval. All measurements were repeated and blood samples were obtained five, 15, 30, 60, 90, 120, 150 and 180 min after albuterol inhalation.

Albuterol Aerosol Administration—Mouth Rinsing and Gargling

In each subject, the same MDI was used on both study days. To eliminate individual variations in the technique of aerosol inhalation, the MDI was activated and the aerosol delivered to the patient by one of the investigators. Drug deposition in the lung was optimized by delivering the aerosol at the open mouth early during a slow (five sec) inhalation from resting lung volume to total lung capacity, followed by a ten sec breath hold at the inspiratory level.

Mouth rinsing and gargling were performed after delivery of each metered dose in the following fashion: immediately after drug inhalation, while holding his/her breath, the patient rinsed the mouth with cold water (4°C) and then gargled while exhaling. The same maneuver was repeated before inhalation of the next aerosol dose. To accommodate individual patient habits, the amount of water used for mouth rinsing was not standardized. However, all rinsings were collected and the quantity measured. A sample was retained and stored in the dark at – 20°C for determination of the albuterol concentration.

Measurements

HR was continuously monitored by an electrocardiographic tracing displayed on an oscilloscope, and BP was measured by auscultation with the pressured cuff method. Spirometry was performed on a dry rolling seal spirometer (model 840, Ohio Medical Products Inc, Houston, TX). All spirometric data reported represent the better of two consecutive measurements. Venous blood samples were kept at room temperature for approximately ten min or until clotting occurred. The samples were then centrifuged for ten min at 2,000 rpm, fibrin clot was removed, the specimen was recentrifuged and the serum collected. Serum samples were stored in capped polyethylene tubes at – 20°C for pooled measurement of serum insulin, glucose, and potassium (K+) concentrations. Serum insulin levels were determined by a radioimmunoassay method (Micromedic insulin RIA KIT, Micromedic Systems Inc, Horsham, PA).

All inhalers were weighed with an electronic toploading balance (Fisher/Answhor model 300 DR, Fisher Scientific, Cincinnati, OH) before and immediately after delivery of the ten metered doses, and the weight changes recorded. Since albuterol accounts for approximately 0.12 percent of the weight of the aerosol, the remainder being Freon propellants, the weight change of the MDI was used to estimate the albuterol dose delivered to each patient. Albuterol concentrations in the rinsing samples collected before (control) and after delivery of the ten metered doses were determined by high pressure liquid chromatography using fluorescence detection (Bio-research Laboratories Ltd., Seneville, Quebec, Canada). The amount of albuterol removed by mouth rinsing and gargling was calculated by multiplying the albuterol concentration by the quantity of the rinsing.

Statistical Analysis

Data were analyzed using Student’s two-tailed t-test for paired data. The various post-treatment values were compared with the mean value of the two pre-treatment control measurements. In a similar fashion, measurements obtained before and at the various times after albuterol administration on one study day were compared with the corresponding values on the other day. A p value of <0.05 was considered significant.

RESULTS

The calculated mean dose (± SD) of albuterol delivered to each of eight patients by ten activations of the MDI was 1,065 (±172) µg on the control day (albuterol alone) and 1,038 (±90) µg on the albuterol/mouth rinsing day (p>0.2). The average amount of water used for mouth rinsing and gargling, determined in seven of the eight patients, was 390 ml (range 290 to 620 ml). Table 1 individually lists the calculated dose of albuterol delivered and the measured drug amount washed out by mouth rinsing in these seven patients. On an average, the procedure removed 24 percent of the calculated aerosolized drug dose, but the amount washed out varied considerably between individual patients. There was no correlation between the quantity of water used for mouth rinsing and the percentage of the total dose recovered in the rinsings (r = 0.49, p>0.1). No measurable amount of albuterol was
Table 1—Calculated Albuterol (ALB) Dose Aerosolized by Ten Activations of MDI, and Measured Amount of ALB Washed Out with Mouth Rinsing and Gargling, in Each of Seven Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>ALB aerosolized (µg)</th>
<th>ALB washed out (µg)</th>
<th>ALB washed out/ aerosolized (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1252</td>
<td>456</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>1008</td>
<td>224</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>977</td>
<td>81</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>1004</td>
<td>312</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>1038</td>
<td>357</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>974</td>
<td>111</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>1045</td>
<td>263</td>
<td>25</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1043 ± 96</td>
<td>258 ± 133</td>
<td>24 ± 11</td>
</tr>
</tbody>
</table>

detected in the control (pre-treatment) mouth rinsings.

The effect of ten consecutive metered albuterol doses delivered with and without mouth rinsing on pulmonary function parameters (FEV₁, FVC), HR and serum glucose and K⁺ concentrations are listed in Table 2. The effect of albuterol on serum insulin, which in our study was the most sensitive metabolic parameter, and on BP are illustrated in Figures 1 and 2. Inhaled albuterol induced highly significant changes from the pre-treatment control values in all measured spirometric, hemodynamic and metabolic parameters. Except for serum K⁺, significant effects of albuterol were observed as early as five min after drug inhalation. Peak changes from the control measurements for all parameters occurred between five and 30 min after treatment: FEV₁ +20 percent, FVC +5 percent, HR +23 percent, BP (systolic) +11 percent, BP (diastolic) −23 percent, insulin +175 percent, glucose +17 percent and K⁺ −5 percent.

Changes similar in magnitude, time of onset, and duration of action were observed when albuterol inhalation was combined with mouth rinsing and gargling. At no time during the three-hour post-treatment period did we observe any significant difference for any measured parameter between the two study days.

**Discussion**

The present investigation was designed to estimate the extent of cardiovascular and metabolic side effects associated with the inhalation of a large dose of aerosolized albuterol and to evaluate the effectiveness of mouth rinsing and gargling in reducing the magnitude of these systemic drug effects.

Aerosol penetration into the human lung depends directly on the pre-treatment airways caliber, as assessed by spirometry. Consequently, to ensure that any differences observed between the two testing days were not due to variations in the depth of aerosol penetration into the lungs, we elected to study patients with mild bronchial asthma and relatively stable airways function other than patients with more severe and unstable levels of airways obstruction. Because our patients were able to avoid the use of bronchodilators for a prolonged time period before, as well as during the study, an influence of chronic maintenance therapy which could have affected our results in any of several ways was safely eliminated. On the other hand, the data presented here might not accurately reflect changes that could have occurred had we studied severely obstructed or chronically medicated patients.

Inhalation of ten consecutive metered doses of albuterol led to the expected highly significant and prolonged improvements in FEV₁ and FVC. In addition, an albuterol dose of this magnitude induced significant changes in the measured metabolic and

**Table 2—Effect of Ten Metered Doses of Albuterol, Delivered With and Without Mouth Rinsing and Gargling, on Spirometry, Heart Rate, Serum Glucose and Potassium Levels in Eight Patients**

<table>
<thead>
<tr>
<th>Time* (min)</th>
<th>5</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, ALB</td>
<td>3.33±0.33</td>
<td>3.92±0.45†</td>
<td>3.96±0.51†</td>
<td>4.00±0.48†</td>
<td>3.96±0.49†</td>
<td>3.97±0.48†</td>
<td>3.93±0.54†</td>
<td>3.89±0.47†</td>
</tr>
<tr>
<td>FEV₁, ALB+MRG</td>
<td>3.42±0.47</td>
<td>3.98±0.44†</td>
<td>3.98±0.46†</td>
<td>4.04±0.46†</td>
<td>4.07±0.46†</td>
<td>4.07±0.46†</td>
<td>4.07±0.50†</td>
<td>3.99±0.40†</td>
</tr>
<tr>
<td>FVC, ALB</td>
<td>4.84±0.35</td>
<td>5.06±0.57†</td>
<td>5.09±0.60†</td>
<td>5.09±0.58†</td>
<td>5.06±0.61†</td>
<td>5.07±0.60†</td>
<td>5.05±0.58†</td>
<td>5.06±0.64†</td>
</tr>
<tr>
<td>FVC, ALB+MRG</td>
<td>4.85±0.02</td>
<td>5.11±0.53†</td>
<td>5.13±0.64†</td>
<td>5.14±0.56†</td>
<td>5.12±0.52†</td>
<td>5.13±0.53†</td>
<td>5.10±0.55†</td>
<td>5.11±0.35†</td>
</tr>
<tr>
<td>HR, min⁻¹, ALB</td>
<td>61±11</td>
<td>75±10†</td>
<td>75±10†</td>
<td>75±10†</td>
<td>75±10†</td>
<td>75±10†</td>
<td>75±10†</td>
<td>75±10†</td>
</tr>
<tr>
<td>HR, min⁻¹, ALB+MRG</td>
<td>61±11</td>
<td>77±9†</td>
<td>75±7†</td>
<td>75±9†</td>
<td>72±9†</td>
<td>70±9†</td>
<td>68±9†</td>
<td>67±9†</td>
</tr>
<tr>
<td>Glucose, mg/dL⁻¹</td>
<td>89±5</td>
<td>96±7</td>
<td>104±6†</td>
<td>100±6†</td>
<td>100±9†</td>
<td>102±7†</td>
<td>98±7†</td>
<td>96±7†</td>
</tr>
<tr>
<td>Glucose, mg/dL⁻¹, ALB+MRG</td>
<td>90±7</td>
<td>96±8†</td>
<td>106±11†</td>
<td>106±12†</td>
<td>104±12†</td>
<td>102±13†</td>
<td>98±9†</td>
<td>97±8†</td>
</tr>
<tr>
<td>K⁺, ALB</td>
<td>3.9±0.2</td>
<td>3.9±0.2</td>
<td>3.8±0.2</td>
<td>3.7±0.2†</td>
<td>3.7±0.2†</td>
<td>3.8±0.1</td>
<td>3.7±0.2</td>
<td>3.8±0.1</td>
</tr>
<tr>
<td>K⁺, ALB+MRG</td>
<td>3.8±0.2</td>
<td>3.8±0.2</td>
<td>3.6±0.2</td>
<td>3.6±0.2†</td>
<td>3.6±0.2†</td>
<td>3.6±0.2†</td>
<td>3.6±0.2†</td>
<td>3.6±0.2†</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; HR = heart rate; K⁺ = potassium.

*Time scale represents minutes after inhalation of albuterol without (ALB) and with mouth rinsing and gargling (ALB + MRG). All values are mean ± SD. Control values are average of two measurements.
†p<0.01, different from control state.
‡p<0.05, different from control state.
FIGURE 1. Serum insulin in the control (CTL) state and at various times after inhalation of ten metered doses of albuterol delivered with (interrupted line) and without (solid line) mouth rinsing and gargling in eight patients. Values are mean ± SEM. Different from average of two CTL measurements *p<0.05, †p<0.01.

FIGURE 2. Blood pressure in the control (CTL) state and at various times after inhalation of ten metered doses of albuterol delivered with (shaded columns) and without (open columns) mouth rinsing and gargling in eight patients. Values are mean ± SEM. Different from average of two CTL measurements *p<0.05, †p<0.01.
cardiovascular parameters, all of which are under the direct or indirect control of the beta adrenergic system. For example, the observed increases in serum glucose and insulin concentrations are the expression of direct beta, adrenergic stimulation of liver glycogenolysis and of insulin secretion by the pancreatic beta cells. The fall in serum K+ reflects a beta, adrenoceptor-mediated shift of K+ from the extracellular to the intracellular compartment. Although the K+ shift could be due in part to the increased insulin level, the observation that intravenously-administered albuterol affects the plasma K+ concentration in patients with type 1 diabetes mellitus to a similar extent as in nondiabetics suggests that the effect of insulin on changes in K+ homeostasis associated with beta, adrenergic stimulation is minor. The observed changes in pulse pressure and HR are due to a combination of albuterol-induced peripheral vasoconstriction and reflex, or direct cardiac stimulation. Thus, aerosolized albuterol in the dose delivered to our patients effected changes in metabolic and cardiovascular parameters in the same direction as those reported to occur with continuous or slow bolus intravenous administration of the drug.

Our patients performed mouth rinsing and gargling twice after each of ten inhalations of metered dose albuterol. To decrease the possibility of early drug absorption across the oral mucosa, they initiated mouth rinsing with cold water at the earliest possible moment, i.e., during the ten sec breath hold after each inhalation. We used cold water (4°C) to induce local vasoconstriction for the purpose of further delaying the occurrence of systemic drug absorption. The procedure, as it was performed in our study, removed on the average approximately one-fourth of the total albuterol dose delivered, but did not reduce the bronchodilator response, decrease the magnitude, or alter the time course of changes observed in any of the cardiovascular or metabolic parameters. Some physicians recommend that their patients rinse and gargle after inhaling aerosolized adrenergic agents from MDIs because of an alleged beneficial effect of the procedure on the occurrence of muscle tremor associated with the use of sympathomimetic agents. We did not objectively measure the magnitude of muscle tremor associated with inhalation of ten albuterol doses; however, by repeated questioning and clinical observation we determined that this side effect was of minor importance and well-tolerated by our subjects. The muscle tremor perceived by some patients after administration of adrenergic agents is due to an increment of physiologic muscle tremor by beta, adrenoceptor stimulation at the level of the skeletal muscle. Because mouth rinsing and gargling in our study failed to reduce side effects due to the apparent stimulation of receptors located in various organ sys-

tems, a selective beneficial effect of the maneuver on skeletal muscle receptors would be difficult to explain. This study was not designed to investigate the site of drug absorption responsible for the occurrence of systemic side effects. Yet, the rapid onset of hyperglycemia and hyperinsulinemia, as observed with intravenous albuterol administration, suggests early systemic absorption of inhaled drug either by way of the bronchial circulation or by direct diffusion of alveolar deposits across the alveolo-capillary membrane. Because the fraction of the total drug dose which was deposited in the mouth may have been considerably higher than the average of 24 percent which we were able to remove by mouth rinsing and gargling, it is possible that oral or oropharyngeal drug residues may have contributed to these side effects.

Inhalation of ten metered doses of albuterol induced marked improvements in pulmonary function, was subjectively well-tolerated by our young and healthy subjects, and was associated with systemic side effects which are likely to be of minor clinical significance, possibly with the exception of patients with underlying cardiovascular or metabolic disorders. Our data thus suggest that, in patients who do not respond satisfactorily to conventional doses of albuterol and who clinically tolerate a larger dose, the magnitude of systemic cardiovascular and metabolic side effects is not of great concern.

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