

The Bioavailability of Salbutamol in Urine via Volumatic and Nonvolumatic Valved Holding Chambers

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Purpose: Pressurized metered dose inhalers are commonly used in patients with asthma. However, the need to coordinate inhalation with inhaler actuation means that they are not suitable for use per se. Valved holding chamber devices were developed to overcome some of the problems of pressurized metered dose inhalers. Several types of holding chambers of different sizes are available in Iran. This study was designed to compare the effects of 2 commonly used valved holding chambers (Asthm Yar and Dam Yar) in Iran on bioavailability of salbutamol spray and also spirometric parameters in asthmatic patients.

Methods: This was a comparative experimental crossover study. Patients with mild to moderate asthma were entered in this study. Lung function was assessed using a portable spirometer (Spirolab, Progetti, Italy). Spirometric parameters of forced expiratory flow (FEF)_{50%}, FEF_{25–75%}, peak expiratory flow (PEF), forced expiratory volume in the first second of expiration (FEV₁), forced vital capacity (FVC), and FEV₁/FVC were measured. Urinary concentration of salbutamol as an index of pulmonary bioavailability was assayed with high-performance liquid chromatography.

Results: Forty patients (25 women and 15 men) with the mean age of 43.10 ± 12.99 years were studied. Mean ± SD changes of spirometric parameters before and after using Asthm Yar were not significantly different from those of Dam Yar. The relative bioavailability after inhalation with Asthm Yar was significantly higher than after inhalation with Dam Yar ($P = 0.002$).

Conclusions: Although the results indicate that relative bioavailability to the lung after inhalation with Asthm Yar was significantly higher than after inhalation with Dam Yar, its clinical importance should be tested.

Key Words: asthma, valved holding chamber, urinary concentration, salbutamol, spirometry

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The majority of asthmatic patients continue to use pressurized aerosol metered dose inhalers (pMDIs).^{1–3} The need to coordinate inhalation and actuation of inhalers is an important issue.³ Valved holding chambers are introduced to overcome this problem.⁴ It has been shown that inhalation therapy using a pMDI with a valved holding chamber plays a crucial role in the treatment of asthmatic patients.^{3,5} The advantage of drug delivery with valved holding chambers in asthmatic patients is due to their simplicity in use compared with pMDIs without valved holding chambers.⁶ They allow the patients to breathe from a pool of the drug. Also, valved holding chambers decrease the amount of medication deposited in the oropharynx.^{7,8} Finally, valved holding chambers increase the delivery of drug to its target (ie, lungs) while minimizing oral absorption.^{9,10}

Several kinds and diverse sizes of holding chamber are obtainable in the market (eg, Aerochamber, Babyhaler, and Volumatic). Asthm Yar and Dam Yar are 2 frequently used valved holding chambers in Iran. There is no convincing study on the efficacy of valved holding chambers with diverse sizes.^{11,12} Measurements of the lung function were used to compare the efficacy. Furthermore, the concentration of drug excreted in the urine during the first 30 minutes after the start of an inhalation is determined for evaluating the differences in systemic bioavailability. Salbutamol deposited in the lungs is immediately delivered to the systemic circulation and excreted in the urine.¹³ Assessing relative bioavailability of salbutamol to the lung by obtaining a urine sample 30 minutes after an inhalation is reproducible, simple, and effective.¹⁴ The advantages of this method in comparison with others is using the patient's own inhaler, no need for either the ingestion of charcoal or the use of a radiolabel-inhaled marker. Furthermore, it could be used concomitantly with the measurement of the lung function to show the correlation between improved deposition and enhanced spirometry.¹³

Thus, the main objective of this study was to compare urinary salbutamol concentration as a measure of relative

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bioavailability to the lung via the 2 valved holding chambers. Also, clinical efficacy in terms of spirometric parameters with the 2 devices was also evaluated.

MATERIALS AND METHODS

Study Subjects and Setting

Patients who referred to the pulmonary clinic of NRITLD (National Research Institute for Tuberculosis and Lung Disease), Masih Daneshvari Hospital, between the age range of 18 and 60 years were evaluated for study eligibility. The study was approved by Ethical Committee of the Shahid Beheshti University of Medical Sciences. Diagnosis of asthma was made according to the Global Initiative for Asthma definition.¹⁵

Patients were excluded if they had severe asthma, chronic obstructive pulmonary disease, and renal dysfunction (serum creatinine, >1.2 mg/dL or <0.6 mg/dL). Also, smokers and pregnant women, and those who were noncompliant to the study protocol, were excluded. All asthma medications except corticosteroid inhalers were discontinued for at least 12 hours before the study.

Study Design

This was a comparative experimental study, which was approved by the Drug and Therapeutic Committee of the Hospital and the Ethics Committee of the Shahid Beheshti University of Medical Sciences, Tehran, Iran. Written consent was obtained from each patient.

The valved holding chamber devices used in this study were consistent with a polycarbonate volumatic (750 mL, Asthm Yar; Farafan Engineering Company, Tehran, Iran) (Fig. 1) and a polycarbonate nonvolumatic (140 mL, Dam Yar; Fanava Teb Espadana Co, Isfahan, Iran) (Fig. 2) valved holding chambers. Salbutamol 100 μ g per dose pMDIs (Ventalex HFA, Sina Daru, Iran) was used with each valved holding chamber. The washing method was based on what



FIGURE 1. Asthm Yar.



FIGURE 2. Damyar.

Mazhar and Chrystyn¹² have proposed in their study. The valved holding chambers were washed in warm mild detergent, soaked in water, and left to air dry before use. The patients used the devices with mouthpieces.

The first 2 actuations from each pMDIs were fired (primed before use). The pMDIs were pressed firmly into the valved holding chambers.

Patients were educated to exhale the functional residual capacity before actuation, then to inhale slowly and deeply to total lung capacity in 5 to 10 seconds after which hold the breath for 10 seconds,¹⁴ and they practiced the correct inhalation technique of the valved holding chamber used at each step. Four doses of salbutamol were then inhaled via the valved holding chamber (volumatic or nonvolumatic). Subjects voided urination 15 minutes before dosing and then provided a urine sample 30 minutes after the first inhalation.¹⁶ Because urinary excretion is the main route of elimination for both unchanged salbutamol and its sulfate conjugate, quantization of the urinary excretion of salbutamol offers a noninvasive method for determining the bioavailability of the drug using different valved holding chambers.¹⁷ In addition, the urinary assay is extremely precise for salbutamol and its conjugate. So, this methodology provides a reliable technique for assessing aerosol delivery and relative lung bioavailability in asthmatic patients.¹⁷ Patients were instructed to maintain their normal fluid intake. Spirometry was performed 10 minutes after the inhalation.

For bioavailability analysis, each patient was trained to inhale 4 actuations of salbutamol (400 μ g) via Asthm Yar and Dam Yar separately. Patients were randomly assigned to use each of the 2 devices at the first phase, and the other one in the second phase of the study. Urine samples were kept in refrigerator (-20°C) until analysis with high-performance liquid chromatography (HPLC). The person who assayed salbutamol level in urine was blind to the study protocol. The subjects used Dam Yar on the first week (first phase) and then crossed over to Asthm Yar on the second week (second phase).

Spirometric Parameters With Valved Holding Chambers

The change in forced expiratory volume in the first second of expiration (FEV₁) 10 minutes after salbutamol inhalation was the primary outcome measure. Measurements were performed by means of Spiro lab II (Medical International Research, Via del Maggolino, Italy). Individual predicted FEV₁ values were recorded according to the patient characteristics. All measurements were performed by a trained investigator. We calculated the absolute change in values from initial prebronchodilator value. Three measurements were achieved for each patient, and the best one was used in data analysis. Other spirometric parameters that were quantified in the study were forced expiratory flow (FEF)_{50%}, FEF_{25–75%}, peak expiratory flow (PEF), forced vital capacity (FVC), and FEV₁/FVC. All the spirometric measurements were performed as per the American Thoracic Association (ATS) criteria.¹⁸

Sample Analysis

Materials and Reagent

Salbutamol sulfate, the United States Pharmacopeia reference standard, was a donation from Exir Pharmaceutical Company. The internal standard epinephrine hydrochloride was obtained from Daru Pakhsh Company. HPLC grade methanol was used in all the analyses. Ultra pure bioreagent grade sodium dodecyl sulfate and potassium dihydrogen phosphate were purchased from Fluka.

Instruments and Conditions

The HPLC system consisted of a pump, an auto sampler, a fluorescence detector, and a computer system. Also used was a C-18 reversed phase 4.6 × 250-mm analytical column (Waters Symmetry C18; Waters Corp, Milford, MA) and a C-18 3.9 × 20-mm guard column (Waters Sentry Guard Column; Waters Corp, Milford, MA). The mobile phase was composed of methanol and water (60:40 vol/vol) containing 10 mM potassium dihydrogen phosphate and 20 mM sodium dodecyl sulfate as an ion-pair reagent. The mobile phase was adjusted at a pH of 2.95 with 1.0 M phosphoric acid. The flow rate was 1.2 mL/minute, and detection wavelengths were 276 nm for excitation and 609 nm for emission.

Standard Preparation

Duplicate spiked urine standards were prepared at 6 different concentrations using 2 independently prepared stock solutions (A and B) to cover the sample analysis, which ranged from 250 to 2000 ng/mL.

Sample Preparation

The urine sample (1 mL) was added to a 10-mL glass centrifuge tube containing 2 mL of 0.1N hydrochloric acid. The tube was capped with a screw top and then was placed in a boiling water bath for 30 minutes. After cooling, an aliquot of 2 mL of 0.1N sodium hydroxide was added to the sample and vortexed. An aliquot of 10 µL of epinephrine hydrochloride internal standard working stock solution (2.5 µg/10 µL) was added to the resulting solution. The mixture was vortexed and then extracted as described below.¹⁹

Solid-phase silica cartridges were used to extract the urine samples before analysis of the drug and metabolites. The cartridges were prepared in-house by packing silica gel (40–60 µm) into Pasteur pipettes. Glass beads (2.5 mm) were placed at the tip of the Pasteur pipette to act as the bed support, followed by the silica gel (100-mg dry weight) to form a bed depth of approximately 25 mm. The cartridges were conditioned by eluting with 2 mL of methanol under gravity and then washing with 2 mL of water. The urine samples (1 mL) containing the drug and epinephrine as the internal standard were loaded on to the cartridges, which were then washed with 2 mL of water before altering the polarity of the eluting solvent by washing with 1 mL of methanol. The eluate was evaporated to dryness with a stream of oxygen-free nitrogen at room temperature. The residue was reconstituted with 250-µL HPLC mobile phase, and a 100-µL sample was injected onto the chromatographic column. The system was validated for accuracy, precision, and linearity.¹⁹

Calculations

Standard curves were generated by plotting peak-area ratios (salbutamol/internal standard) as a function of salbutamol concentration and by least-squares linear regression analysis for the line of best fit. The final concentration represented the sum of both unchanged salbutamol and its sulfate conjugate.

Statistical Analysis

The analysis of data was performed using statistical package for social sciences (SPSS 17; SPSS, Inc, Chicago, IL). The results were expressed as mean ± SD, and the Student *t* test and the paired *t* test were applied for demographic and spirometric data comparisons. *P* values of <0.05 were regarded as significant.

RESULTS

Forty patients (25 women and 15 men) with a mean ± SD age of 43.10 ± 12.99 years were recruited. Table 1 illustrates detailed demographic data and spirometric results obtained in this study.

There was a significant improvement in the mean spirometric parameters after using each valved holding chamber (*P* < 0.05). However, no significant difference was observed between the 2 valved holding chambers in terms of spirometry improvements.

The concentration of salbutamol recovered in the urine was 1188.84 ± 478.80 ng/mL using Asthm Yar and 926.68 ± 351.95 ng/mL using Dam Yar. The percentage of drug excreted differed significantly between the 2 groups (*P* = 0.002) (Fig. 3; Table 1).

DISCUSSION

To assess if valved holding chambers' volume or size has a role in clinical practice, the response to 400 µg of salbutamol administered by small volume valved holding chamber (Dam Yar) was compared with that obtained with the same dose administered with large volume valved holding chamber

TABLE 1. Detailed Demographic Data and Spirometric Results

Variable	Distribution		P
	Total	Strata	
Age (yr)	43.10 ± 12.99	Male: 44.93 ± 14.07 Female: 43.32 ± 12.56	0.71
Gender	N = 40	Male: 15 Female: 25	NA
Weight (kg)	68.53 ± 13.38	Male: 73.27 ± 9.26 Female: 65.68 ± 14.79	0.08
Height (cm)	163.33 ± 7.91	Male: 170.45 ± 7.70 Female: 159.04 ± 4.00	<0.0001*
FVC† difference‡	5.34 ± 7.45	Asthm Yar: 4.75 ± 6.99 Dam Yar: 6.05 ± 8.00	0.46
FEV ₁ † difference ‡	7.39 ± 5.49	Asthm Yar: 7.54 ± 5.08 Dam Yar: 7.23 ± 5.93	0.53
PEF† difference‡	4.18 ± 13.52	Asthm Yar: 7.10 ± 13.64 Dam Yar: 1.25 ± 12.92	0.054
FEF _{25-75%} † difference‡	16.20 ± 12.49	Asthm Yar: 16.30 ± 12.05 Dam Yar: 16.10 ± 13.06	0.92
FEF _{50%} † difference‡	13.94 ± 11.55	Asthm Yar: 13.45 ± 11.78 Dam Yar: 14.43 ± 11.44	0.64
Preference	6.00 ± 2.58	Asthm Yar: 4.83 ± 2.38 Dam Yar: 7.18 ± 2.23	<0.0001*
SUC (ng/mL)§	Mean: 1057.76 ± 437.86	Asthm Yar Mean: 1188.84 ± 478.80 Minimum: 419.51 Maximum: 2471.95 Dam Yar Mean: 926.68 ± 351.95 Minimum: 264.63 Maximum: 1787.81	0.002*

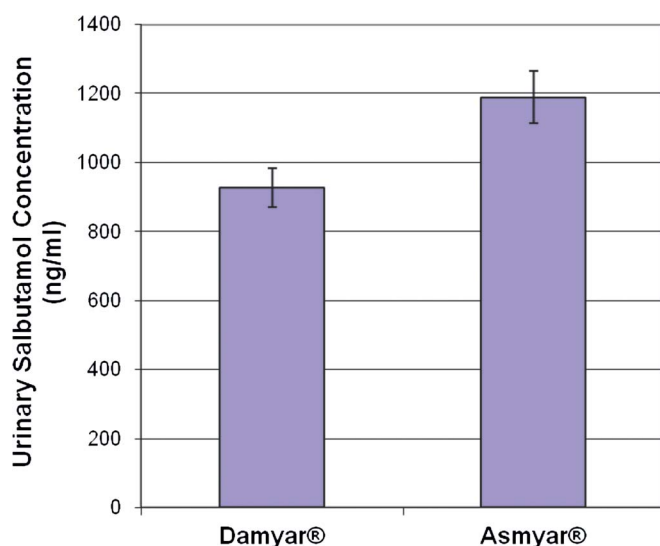
*Significant differences.

†As percentage of the predicted values.

‡Before and after spacer use.

§Salbutamol urine concentration.

FEF, forced expiratory flow; PEF, peak expiratory flow; FVC, forced vital capacity.

**FIGURE 3.** Urinary salbutamol concentration (mean ± standard error) after inhalation via Dam Yar (spacer1) and Asthm Yar (spacer 2).

(Asthm Yar), which are the 2 commonly used valved holding chambers in Iran. Asthm Yar is more bulky compared with Dam Yar, which has a smaller volume, thus is inconvenient to use and carry around.²⁰ The urinary excretion of salbutamol in patients reflects the systemic absorption of the drug deposited in the lower respiratory tract. Furthermore, the urinary assay is highly specific for salbutamol and its conjugate.¹⁴ After 1 and 2 doses of salbutamol from Easibreath in asthmatic patients, the results of measurements of 30-minute urinary salbutamol and the dose of methacholine to reduce the FEV₁ by 20% were in concordance.²¹ The equivalency of these 2 methods and the reproducibility showed that the 30 minutes could be used as an index of lung deposition. These results also confirm the vital role of pharmacokinetic studies in determining the bioequivalence of inhaled products.²²

Based on the results of this study, the amount of excreted salbutamol in the urine 30 minutes after inhalation with Asthm Yar (1188.84 ± 478.80 ng/mL) shows significant difference ($P = 0.002$) in comparison with that excreted after inhalation with Dam Yar (926.68 ± 351.95 ng/mL). Therefore, large volume spacer delivered more drug than smaller one. These results are in consistency with the available reports on better drug

delivery by higher volume spacers.¹⁰ Several in vitro and in vivo studies have shown that different factors affect the dose delivered from a holding chamber and may be responsible for this poor efficiency.^{23,24} These include chamber size, shape, resistance of the valve, dead volume, the use of multiple actuations, inhalation delay, and construction materials, which have influence on the levels of electrostatic charge in the chamber. Electrostatic charge is intrinsic to every plastic device, including plastic spacers, as a result of their nonconducting properties. The charge varies in a random style. The net effect of electrostatic charge is the absorption of aerosol particles onto plastic surfaces of the spacers, leading to a noteworthy reduction in the initial dose available for inhalation and hence the lung dose.²⁵ Approximately 90% of the dose is dumped and swallowed in the oropharyngeal system using pMDIs. However, using spacers would result in the reduction of particle velocity during inspiration and therefore decreases the systemic bioavailability of the drug.¹⁰ Perhaps, Asthm Yar is more efficiently designed that its electrostatic charge might have been less than Dam Yar. Although this hypothesis should be confirmed in the future studies, as mentioned before, these devices were static and washed before use.

In a study by Lipworth and Clark²⁶ in 1998, salbutamol inhalation dose as a MDI was measured via 3 common plastic spacers (Nebuhaler, Volumatic: large volume, and Aerochamber: small volume). The results demonstrated that the large volume spacer (Volumatic) had more drug delivery to the lungs in comparison with Aerochamber and Nebuhaler or using the MDI alone.²⁶ Furthermore, Mazhar and Chrystyn¹² have compared Volumatic (VOL) and Aerochamber Plus VHC (AERO). Data confirmed that Volumatic was more efficient, although the difference was very small. However, our results are consistent with their findings. The increased bioavailability of salbutamol using large volume spacers may be of special interest in patients with poor inhalation technique that could result in improved lung function in this population.¹⁴ Nevertheless, this finding is not consistent in all the studies. In 2005, Walker and Owen²⁰ assessed the effect of spacer volume on drug delivery to children using pressurized inhalers. Unexpectedly, small volume spacer delivered more drug than large volume spacer. It is believed that this is possibly due to the more efficient construction and design of the Aerochamber, as the delivery is normally improved when using large volume spacers.²⁰

In conclusion, although the results indicated that relative bioavailability to the lung after inhalation with Asthm Yar was significantly higher than that after inhalation with Dam Yar, its clinical importance should be tested.

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