

Delivery of glucocorticoids by jet nebulization: Aerosol characteristics and output

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Background: Since inflammation has been identified as a critical factor in the pathogenesis of asthma, use of inhaled glucocorticoids has increased. Because young children are often unable to coordinate properly the use of metered-dose inhalers and no glucocorticoids preparations for nebulization have been approved in the United States, parenteral and intranasal glucocorticoids preparations are occasionally administered by nebulization.

Methods: We examined whether a parenteral preparation (triamcinolone acetonide [TAA]; Kenalog) could be delivered by nebulization. TAA, 1000 µg (0.1 ml), was placed in the nebulizer bowl (MB5 [MeFar, Brescia, Italy] or Pari-Jet [Dura Pharmaceuticals, San Diego, Calif.]), then diluted with 2.9 ml normal saline solution for a total volume fill of 3 ml. Using a laser particle analyzer, high-performance liquid chromatography, and cascade impactor, we examined the percentage of aerosol volume produced with particles in the respirable range of 1 to 5 µm in diameter, actual TAA output (in micrograms) and concentration of TAA contained in the particles within the respirable range.

Results: Laser particle analysis indicated that $34\% \pm 3\%$ (mean $\pm$ SEM) (MB5) and $47 \pm 3\%$ (Pari-Jet) of the total aerosol volume produced were within the respirable range of 1 to 5 µm in diameter, and this remained consistent throughout nebulization. The nebulizer was stopped serially for determination of TAA output with high-performance liquid chromatography. TAA output (1000 µg less the amount in micrograms remaining after nebulization) was essentially complete after 2 minutes with the Pari-Jet and within 4 minutes with the MB5 and totaled 352 ± 19 µg and 367 ± 9 µg, respectively. Finally, cascade impactor studies confirmed that 33.4% of the TAA aerosol generated by the MB5 nebulizer was contained in particles in the respirable range.

Conclusion: Approximately 35% (Pari-Jet) and 37% (MB5) of the initial 1000 µg of TAA was delivered with the two nebulizers tested. The particles generated within the respirable range were limited to 34% (MB5) and 47% (Pari-Jet) of the amount delivered. TAA was equally distributed in the particles generated. The theoretic amount delivered in the respirable range was approximately 12.5% for the MB5 nebulizer on the basis of the cascade impactor and 16.5% for the Pari-Jet (assuming TAA distribution equivalence) of the TAA placed in each of the nebulizers. Additional clinical studies are needed to define efficacy and safety in view of the excipients used in preparing the parenteral preparation. (*J ALLERGY CLIN IMMUNOL* 1995;95:944-9.)

Key words: Triamcinolone acetonide, glucocorticoids, laser particle analyzer, high-performance liquid chromatography, cascade impactor

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Abbreviations used

ECD:	Effective cutoff diameter
GSD:	Geometric standard deviation
HPLC:	High-performance liquid chromatography
LPA:	Laser particle analyzer
MMAD:	Mass median aerodynamic diameter
TAA:	Triamcinolone acetonide
VMD:	Volume median diameter

Asthma is an inflammatory disease characterized by edema, airway smooth muscle constriction, and an infiltration of the bronchial mucosa and submucosa with lymphocytes and eosinophils.¹ Because of the inflammatory nature of the disease, inhaled glucocorticoids have become a major first-line therapy in the treatment of asthma.² Glucocorticoids are available for inhalation from metered-dose inhalers; however, young children (especially those <5 years of age) are often unable to coordinate their use properly. Glucocorticoid preparations for nebulization are not currently available in the United States. Because of this, some physicians have nebulized glucocorticoid preparations intended for intranasal or parenteral administration to deliver glucocorticoid aerosol to children with severe asthma.

Particles greater than 15 μm , and for the most part those greater than 10 μm in diameter, are primarily deposited in the oropharynx by inertial impaction and swallowed; thus they do not reach the desired site in the lungs.³ All particles denser than air have a downward force caused by gravity, which results in sedimentation. Sedimentation increases in the last five to six generations of bronchi, where air velocity is at its lowest.⁴ Particles less than 1 μm in diameter are usually exhaled unless the patient holds his or her breath and do not contribute significantly to aerosol therapy. Thus particle size is a critical factor determining the site of deposition, with the optimal particle size for delivery of medications to the lung being approximately 1 to 5 μm in diameter.⁵

The three goals of this investigation were to determine (1) whether triamcinolone acetonide (TAA) left the nebulizer, (2) whether the nebulized cloud contained a sufficient percentage of particles within the respirable range, and (3) whether the particles within the respirable range contained glucocorticoid. TAA was chosen for our study because it is inexpensive and available in a sufficiently concentrated form to permit delivery of

a therapeutic dose of medication. It is also occasionally employed as a nebulized glucocorticoid, although not approved for this use.

METHODS

The study protocol examined the nebulizer output and aerosol characteristics of Kenalog Injection Suspension (TAA, E. R. Squibb & Sons Inc., Princeton, N.J.), a parenteral preparation. Kenalog Injection Suspension (TAA) is available in a concentration of 1000 μg per 0.1 ml. A total of 1000 μg TAA, or 0.1 ml, was added to 2.9 ml normal saline solution for a total volume fill of 3.0 ml. Previous studies investigating albuterol and other bronchodilators have shown that different initial volume fills can affect output of medication and aerosol characteristics.^{6,7} We therefore limited this investigation to a 3 ml fill volume. To minimize potential variability in glucocorticoid concentrations, a single lot of Kenalog Injection was used.

Nebulizers

Two nebulizers were used: the MB5 (MeFar, Brescia, Italy) and the Pari-Jet (Dura Pharmaceuticals, San Diego, Calif.) nebulizers. The Pari-Jet nebulizer was selected because it provided rapid and efficient delivery of a solution in an extensive nebulizer comparison study.⁸ Efficiency was based on the percentage of particles within the respirable range of 1 to 5 μm and the time required to deliver these particles. The construction of this nebulizer facilitated recovery of the remaining glucocorticoid preparation for quantitative analysis of residual glucocorticoid. The MB5 nebulizer was chosen for testing because it is commonly used and because its construction facilitated recovery of residual TAA. The nebulizers were driven by a PulmoAide compressor (Devilbiss Co., Somerset, Pa.) at a flow rate of 6.3 L/min.

Drug delivery

Drug delivery during intervals from 30 seconds to 8 minutes was tested. The nebulizers were weighed before nebulization and at each time point to determine the remaining volume. After the nebulizers were sampled at these intervals for glucocorticoid determinations, they were emptied, dried, and rerun from the initial volume and zero time to the next sampling time.

Drug analysis

At each time point remaining glucocorticoid was rinsed from the nebulizer with 2 ml of acetonitrile/methanol (1:1) and collected for analysis by high-performance liquid chromatography (HPLC).⁹ For this assay we employed a silica gel column (Zorbax, Sil Dupont Chemistry, Wilmington, Del.) and a mobile phase containing relative proportions of 400:200:350:15 of methylene chloride, ethylene dichloride, heptane, and glacial acetic acid. Ethanol was added in varying quantities (22 to 40 ml/L of mobile phase) to

TABLE I. Cascade impaction analysis for MB5 nebulizer (expressed as amount of drug recovered per stage)

Stage	ECD (μm)	Amount (ng)†	% of total
1	5.0	11,689 ± 55	65.1
2	4.0	2442 ± 20	13.6
3	3.0	1635 ± 32	9.1
4	1.8	1260 ± 43	7.0
5	1.0	657 ± 19	3.6
6	0.4	236 ± 14	1.3
7	0.25	30 ± 3.5	<1.0
Total of all stages		17,949 ± 828	100.0

*Calibrated and validated by cascade impactor.

†Mean ± SEM of five experiments.

adjust the retention time for the glucocorticoid to approximately 4 minutes. The intraday and interday coefficient of variation of this system is less than 5%, and the lower limit for glucocorticoid detection is 5 ng/ml.¹⁰ No extraction was performed, and the TAA was diluted in mobile phase and injected directly. Standards for TAA were performed with each run, and test concentrations were derived from a standard curve. Drug analysis is represented by the following equation: Amount Delivered = Initial Dose (1000 μg) – Amount Remaining in Nebulizer.

Particle size

The distribution of particles by size within the aerosol was determined with a laser particle analyzer (LPA) (model CSASP-100-HV, Particle Measuring Systems, Boulder, Colo.), which measures particles ranging from 0.5 to 32 μm in diameter.¹¹ The aerosol produced by the nebulizer was analyzed continuously. Particles pass through a laser beam and the light is bent or refracted. Larger particles refract light at a greater angle, and particles are sized by their angle of refraction. When two particles pass through the laser beam at the same time or when a particle does not pass completely through the beam, light is refracted at a greater angle and therefore oversized. The analyzer detects these events, known as "coincidence errors," and excludes these data from calculation. Data derived from the particle analysis is represented by the following equation: Estimated Amount Available to Lung = (Amount Delivered) × (Fraction in Respirable Range).

To simulate patient use of nebulizers, we adjusted the flow rate of the LPA to be equivalent to that of typical inhalations. It has been reported that adult patients inhale at a rate of 0.7 L/sec.¹¹ The LPA has been modified to withdraw air at 0.655 L/sec. It is important to simulate the patient's inspiratory rate because flow rate changes can modify characteristics of the aerosol that exits the nebulizer.¹² Our results can be correlated to

actual patient use when the respiratory rate and inspiratory time are known.

Drug delivery in the respirable range

A cascade impactor (MCR No. 02-140, In-Tox, Albuquerque, N.M.) was used with the MB5 nebulizer to analyze the amount of drug contained in the various sized particles. Although the LPA determines the particle sizes within the aerosol, it does not determine whether the particles contain glucocorticoid. The cascade impactor separates the aerosol according to size through a series of stages containing jets and an impacting surface placed immediately downstream of the jets. For data analysis stages 2 through 5 were used on the basis of the desired particle range of 1 to 5 μm. The effective cutoff diameter (ECD) for each stage is included in Table I. The upper and lower boundaries for the size interval collected by an impactor stage were considered to be those particle sizes at which 50% of the particles were collected, termed the stage ECD. Therefore the size interval to which material on stage 3 of the impactor sample was assigned was defined by the ECD of stage 2 as an upper limit and by the ECD of stage 3.

To avoid variability resulting from operator technique or environmental factors (i.e., ambient temperature and humidity), runs were sequenced randomly and repeated at least 10 times by a single operator. Ambient temperature was maintained at 65° to 75° F and was constantly monitored. Relative humidity was maintained within a range from 30% to 40% saturation and was continuously monitored with a hygrometer. Potential differences in nebulizer output were minimized by using a single nebulizer of each type, which was tested and determined to have consistent output rates and aerosol characteristics for a given product.

Data analysis

The aerosol characteristics, specifically volume median diameter (VMD), geometric standard deviation (GSD), and the percentage of the total aerosol within the respirable range of 1 to 5 μm were determined with data generated by the LPA. The LPA counts particles within various diameter ranges. From these data the total volume of the aerosol contained within a given diameter range (with the use of mean diameter within that range) was calculated by a computer program (Xtree, Phoenix Systems) by the following equation: Volume = $\frac{4}{3}\pi r^3$; where r is the radius. The cumulative percentage of the total volume versus the diameter of the particles was used to derive VMD and GSD. The VMD is the aerodynamic diameter above and below which 50% of the mass of the particles is contained. GSD is calculated from particle diameter at 84% fraction of total volume delivered divided by VMD.¹³ From this profile the percentage of total aerosol in the respirable diameter range of 1 to 5 μm was calculated.

Delivery time was determined with the LPA by observing the amount of time required to arrive at approximately a 10-fold drop in the number of particles generated. Nebulizer output was measured by weighing the nebulizer with solution before nebulization and then at given time points after nebulization. Output was determined by the following equation: $\text{Output} = (\text{Weight of Nebulizer} + \text{Glucocorticoid Preparation} + \text{Diluent before Nebulization}) - (\text{Weight of Nebulizer} + \text{Remaining Solution with Glucocorticoid})$. This equation assumes that the specific gravity of each preparation and diluent is 1.0, which was verified. The amount of drug remaining in the nebulizer was measured by HPLC. From this we were able to estimate "inhaled dose" of glucocorticoid, which was defined as the potential amount of TAA delivered to the lung by the following equation: $\text{Inhaled Dose} = (\text{Initial Amount of Glucocorticoid in Micrograms} - \text{Amount of Glucocorticoid Remaining in Nebulizer in Micrograms}) \times (\text{Percentage of Total Output in Respirable Range})$. Descriptive analysis was applied to delivery time, nebulizer output, VMD, GSD, percentage of the total aerosol in the respirable range, and potential lung dose. Data are presented as mean $\pm$ SEM.

RESULTS

Drug delivery

We first addressed the question whether TAA leaves the nebulizer. The MB5 nebulizer was run a total of 17 times each at 30 seconds, and at 1, 2, 4, and 6 minutes, and eight times at 8 and 10 minutes. A total of 10 nebulizations were performed at 0, 1, and 2 minutes, respectively, for the Pari-Jet nebulizer. Total output (in micrograms) versus time (in minutes) is presented in Fig. 1. Analysis of the TAA remaining in the respective nebulizers demonstrated that $352 \pm 19 \mu\text{g}$ TAA from the Pari-Jet at 2 minutes and $367 \pm 9 \mu\text{g}$ TAA from the MB5 nebulizer at 4 minutes was delivered from the original starting dose of $1000 \mu\text{g}$ TAA, with the remainder of glucocorticoid recoverable from the nebulizer bowl. The Pari-Jet nebulizer completed delivery of glucocorticoid by 2 minutes whereas the MB5 nebulizer took almost 4 minutes to complete glucocorticoid delivery (Fig. 1). However, total delivery of TAA was similar for the two nebulizers. Further nebulization beyond these times did not increase the total amount of TAA delivered by either nebulizer.

Particle size production

The second question addressed was the size distribution of particles and the percentage of particles in the respirable range of 1 to $5 \mu\text{m}$. A total of 57 and 36 runs from the MB5 and Pari-Jet nebulizers were performed. LPA determined that

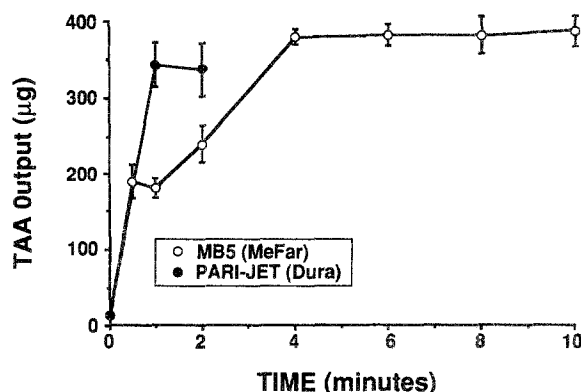


FIG. 1. Comparison of total output versus time of TAA with use of two nebulizers. MB5 (○) included 17 runs at each time point between 0 to 6 minutes and eight runs at 8 and 10 minutes. Pari-Jet (●) included 10 runs at 0, 1, and 2 minutes. Analysis of residual TAA in respective nebulizers demonstrated approximately $352 \pm 19 \mu\text{g}$ at 2 minutes (Pari-Jet) and $367 \pm 9 \mu\text{g}$ at 4 minutes (MB5) of original starting dose of $1000 \mu\text{g}$ TAA that had been delivered. Data are presented as mean $\pm$ SEM.

$34\% \pm 3\%$ (MB5) and $47\% \pm 3\%$ (Pari-Jet) of the total aerosol volume produced was within the respirable range of 1 to $5 \mu\text{m}$. The actual particle size production remained constant throughout nebulization. The VMD for the MB5 nebulizer was $6.0 \mu\text{m}$ and was assumed to be the equivalent of the mass median aerodynamic diameter (MMAD), and the GSD was 1.3. For the Pari-Jet nebulizer VMD was $4.6 \mu\text{m}$ and GSD 1.4.

Glucocorticoid content within the particles

A cascade impactor was used to determine the amount of TAA contained in particles of various sizes. With the use of the MB5 nebulizer in combination with a cascade impactor, TAA was recovered and analyzed by HPLC. Stages that collected particles with ranges from 1 to $5 \mu\text{m}$, stage 2 to 5, were considered to represent particles in the respirable range. The percentage of TAA in the respirable range was determined by the following analysis: $\text{Nanograms of TAA (Stages 2 to 5)} \div \text{Total Nanograms Collected} = 33.4\%$ (Table I). At a flow rate of 2 L/min, only a small portion of the actual nebulized cloud generated at 6.3 L/min was drawn into the cascade impactor.

On the basis of HPLC determination of TAA, laser and cascade impactor analysis of particle size distribution, and glucocorticoid concentration, the inhaled dose was estimated at $124.8 \mu\text{g}$, or 12.5% of the initial dose for the MB5 nebulizer, and $165.4 \mu\text{g}$, or 16.5% of the original TAA dose of $1000 \mu\text{g}$ for the Pari-Jet nebulizer, delivered to the oro-

pharynx and lungs of the patient. These figures are based on the following assumptions. Beginning with 1000 μg of TAA, depending on the nebulizer, 35% (Pari-Jet) or 37% (MB5) left the nebulizer as an aerosol. Of this $367 \pm 9 \mu\text{g}$ (MB5) and 352 ± 19 (Pari-Jet) μg of TAA, approximately 34% (MB5) and 47% (Pari-Jet) of the particles were in the respirable range of 1 to 5 μm , for a total of 124.8 (MB5) or 165.4 μg (Pari-Jet) of the original 1000 μg TAA. We performed only cascade impaction studies with the MB5 nebulizer and made the assumption that TAA was similarly distributed in the nebulizer output for the MB5 and the Pari-Jet nebulizers.

DISCUSSION

Treatment of asthma with inhaled glucocorticoids is now generally accepted as a first-line therapy. With no currently available preparations for nebulization in the United States, physicians have increasingly employed parenteral and nasal glucocorticoid preparations such as TAA (Kenalog), a parenteral preparation, or flunisolide (Nasalide) and beclomethasone dipropionate (Vancenase AQ and Beconase AQ) nasal preparations delivered by nebulization in an attempt to control airway inflammation in children too young to use metered-dose-inhalers. Several studies have evaluated nebulized flunisolide in patients with severe bronchopulmonary dysplasia and reported improvement in respiratory symptoms. In one study Konig et al.¹⁴ administered flunisolide in doses ranging from 0.75 ml (187 μg) four times daily to 1 ml (250 μg) four times daily. The dose was adopted because in previous experience this amount was safe (including absence of changes in adrenal function tests) and effective. The solution was delivered by jet nebulization at a flow rate of 6 L/min either with a face mask or by the "blow by" technique. However, flunisolide (250 $\mu\text{g}/\text{ml}$) is not very concentrated, and with only 25 ml per container it becomes expensive. To administer 250 μg of this glucocorticoid daily, one would have to use a full container of flunisolide solution every 6 days. Beclomethasone dipropionate is a microcrystalline suspension that becomes extremely viscous during nebulization. The Appendix provides a summary of excipients in the various preparations. Budesonide is currently available in Europe and Asia in a nebulizable preparation but is presently not available in the United States.

In our evaluation TAA was selected because it is occasionally used in clinical practice under nonapproved conditions. However, no published clinical

studies to verify efficacy exist. TAA is more concentrated and is relatively inexpensive, making it an attractive formulation for nebulized therapy. Our study indicated that 12.5% (MB5) and by assumption 16.5% (Pari-Jet) of TAA aerosolizes in the respirable range of 1 to 5 μm when mixed with normal saline solution. The major portion of the glucocorticoid output, with the MB5 nebulizer, occurred within the first 4 minutes of nebulization with a significant dropoff in amount delivered beyond this point. The Pari-Jet nebulizer delivered the drug much more rapidly, with drug output essentially completed by 2 minutes. The addition of 3 ml of normal saline solution to the nebulizer bowl at the end of 4 minutes did not result in mobilization of any significant additional TAA. One possible explanation for the failure to mobilize additional drug is that the steroid that is maintained in suspension may aggregate and form insoluble particles during nebulization, diminishing ultimate output. Another possible explanation is that the TAA may simply bind to the nebulizer bowl.

Optimal aerosol delivery depends on particle size. The optimal MMAD for aerosol therapy is 1 to 5 μm . The VMD in our study, assumed to be the equivalent of the MMAD, was 6.0 μm with a GSD of 1.3 for the MB5, indicating favorable respirable range particle production. For the Pari-Jet nebulizer VMD was 4.6 μm and GSD 1.4, indicating slightly more favorable production of particles in the respirable range than the MB5 nebulizer. Such particles are readily delivered to and retained in the intrathoracic cavity.¹⁵ A previous study examining upper airway deposition with particle size curves for the adult and child showed they were in good agreement when similar states of physiologic activity are compared. The authors concluded that it seemed reasonable to assume nasal aerosol deposition for children is identical to the adult at the same state of breathing. One can then estimate the percentage of any particle size that is able to penetrate the child's nasal airway and reach the more distal regions of the lung.¹⁶

Our results with TAA indicate that its delivery from these two nebulizers, overall particle size distribution, and concentration of glucocorticoid within the particles theoretically allows delivery of a therapeutic dose of glucocorticoid to the lungs. Clinical studies are needed to define efficacy and safety because TAA is not approved for nebulized administration. It contains excipients such as benzyl alcohol and hydrochloric acid that have been previously reported to induce bronchospasm.¹⁷

Although the use of this technique for aerosol delivery of glucocorticoid in children is increasing, there are no data on the properties of available glucocorticoid preparations administered by nebulization. This study characterizes TAA when delivered by these two nebulizers under conditions of adult inhalation flow rate. Further investigation into the variables involved in nebulizer delivery of TAA and other glucocorticoids will provide important information in developing a useful product for the young patient with asthma. In addition, this study provides a model for analysis of medications considered for nebulized delivery.

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APPENDIX

Excipients of available nasal and parenteral glucocorticoid preparations (derived from product information inserts)

Beclomethasone dipropionate (Vancenase AQ Nasal Spray, Schering Corp., Kenilworth, N.J., and Beco-nase AQ Nasal Spray, Allen & Hanburys, Div. of Glaxo Inc., Research Triangle Park, N.C.) is a monohydrate, very slightly soluble in water but very soluble in chloroform and freely soluble in acetone and alcohol. It is a microcrystalline suspension, white to creamy white in appearance, and is supplied as an aqueous medium containing microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and 0.25% phenylethyl alcohol. Hydrochloric acid may have been added to adjust pH.

Flunisolide (Nasalide Nasal Solution, Syntex Laboratories Inc., Palo Alto, Calif.) is a white to creamy white crystalline powder. It is soluble in acetone, sparingly soluble in chloroform, slightly soluble in methanol, and practically insoluble in water. It is supplied in a solution of propylene glycol, polyethylene glycol 3350, citric acid, sodium citrate, butylated hydroxyanisole, edetate disodium, benzalkonium chloride, and purified water.

Triamcinolone acetonide (TAA; Kenalog Injection Suspension, E. R. Squibb & Sons Inc., Princeton, N.J.) is a sterile aqueous suspension, which also contains sodium chloride for isotonicity, 0.9% benzyl alcohol as a preservative, 0.75% carboxymethylcellulose sodium, and 0.4% polysorbate 80. Sodium hydroxide and hydrochloric acid may have been added to adjust pH between 5.0 and 7.5.