Metered Dose Inhaler Therapy for Asthma, Bronchitis, and Emphysema

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This review addresses the use of the metered dose inhaler (MDI) to administer aerosol therapy in the treatment of asthma, bronchitis, and emphysema. Studies have shown that physicians' prescribing patterns for use of the inhaler have been inconsistent with optimal therapy. Furthermore, the medical literature suggests that the metered dose inhaler should replace the jet nebulizer in hospital and outpatient settings as a more efficient and cost-effective treatment method.

All classes of aerosol drugs are now available for administration by the MDI. Reports suggest that patients whose conditions do not respond to treatment administered by the MDI may improve following instruction in the proper method of using the inhaler or by increasing the recommended dosage of medication for those receiving β-adrenergic, anticholinergic, and glucocorticoid drugs. A consensus now recommends that aerosol glucocorticoids be considered the primary method of therapy for asthma; however, the effectiveness of glucocorticoids in the treatment of bronchitis and emphysema has not been determined. Although available data do not prove that drugs used in the treatment of asthma increase mortality, further study is recommended in view of the potential toxicity of these drugs.

Key words. Administration, inhalation; nebulizers and vaporizers; asthma; bronchitis; lung diseases, obstructive. *J Fam Pract 1992; 34:485-492.*

Asthma and chronic obstructive pulmonary disease (COPD), eg, bronchitis and emphysema, afflict 24 million Americans; these patients spend more than $1 billion annually on treatment.[1] These chronic pulmonary diseases continue to pose a serious problem to the health care system in the United States, despite medical research that has improved our understanding of their pathophysiology and led to the development of an extensive array of effective medications.[2–4]

A survey of physician prescribing patterns demonstrates that aerosol drugs represent the most commonly used treatment of obstructive lung diseases in hospitals.[5] Increased awareness of the potential benefits that can be derived by more effective use of the metered dose inhaler (MDI) to administer aerosol therapy in both hospital and outpatient settings has the potential to simultaneously decrease the cost of medical care and reduce the morbidity and mortality of these diseases.

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Therapeutic Aerosols

All classes of therapeutic aerosol drugs are currently available for administration by the MDI. An understanding of their pharmacological actions is prerequisite to improving the therapy of patients with asthma and COPD.

β-Adrenergic Drugs

β-Adrenergic drugs stimulate β-receptors in the airway, resulting in smooth muscle relaxation and bronchodilation, enhancement of mucociliary clearance, and attenuation of prostaglandin-induced bronchospasm. The molecular mechanisms by which relaxation is induced have been well studied: an increase in cyclic AMP activates specific kinases, leading to a decrease in intercellular calcium ion concentration and an inhibition of myosin phosphorylation.[6,7]

Effective doses of these drugs result in very low blood levels (billionths of a gram), and, consequently, the chance of developing systemic side effects is remote. Potential side effects occurring at higher dosage levels are sympathetic stimulation, decreases in arterial oxygen ten-

Table 1. Therapeutic Agents Available in Metered Dose Inhaler

Drug	Peak Effect* (minutes)	Duration of Effect* (hours)	Average Cost per Inhaler** ($)	Pregnancy Category (FDA)
β-Adrenergic				
Isoproterenol	5–15	1–2	23.63	C
Isoetharine	15–60	2–3	26.98	C
Metaproterenol	30–60	3–4	20.23	C
Terbutaline	60	4	22.10	B
Albuterol	30–60	4	24.16	C
Bitolterol	30–60	5	18.00	C
Pirbuterol	30–60	5	18.82	C
Anticholinergic				
Ipratropium	60–120	3–6	26.80	B
Biscromones				
Cromolyn	15–30	2–6	37.15	B

**Data from Physicians' Desk Reference,[13] Drug Evaluations,[15] and Bar-Yishay et al.[16]*
***Derived from pharmacy price quotes.*
Pregnancy Category B denotes no evidence of risk in humans. (Fetal risk evaluation: animal studies +, human studies −; or animal studies −, human studies not done.) Category C denotes that risk cannot be ruled out. (Fetal risk evaluation: animal studies + or lacking; human studies lacking.) FDA denotes Federal Drug Administration.

sion in the immediate post-therapy period, cardiac arrhythmias, and hypoglycemia.[6,8]

These agents are indicated for the short-term relief of bronchoconstriction and are the treatment of choice for acute exacerbations of asthma. Increased dosages are particularly useful in acutely ill patients. For example, some have treated such patients by prescribing two to four puffs of a β-adrenergic drug up to six times daily. Life-threatening episodes in the emergency department may require four puffs over 2 minutes followed by one puff per minute until dyspnea is relieved or side effects limit further use. Increased doses may seem better justified when one considers that doses delivered by jet nebulizer are fivefold to tenfold greater than the usual two puffs from an MDI.[9,10] Patients receiving increased dosages should be monitored closely for the presence of side effects. Ideally, elective measurement of cumulative or noncumulative dose response curves in the pulmonary function laboratory will provide an estimate of a patient's maximal tolerable dosage.[11,12]

The prescribing of higher than usual dosages raises questions of safety. One must consider, however, that problems related to inadequate treatment with low dosages probably exceed the toxic problems associated with higher, more effective dose levels.

The Food and Drug Administration's rating of the risk of use of these drugs in pregnant women and the literature provide guidance concerning the teratogenic potential of these drugs[13,14] (Table 1).

Patient Selection

Pulmonary function studies performed before and after bronchodilator administration are helpful in selecting responsive patients. Evidence of a 12% to 25% improvement in forced expiratory volume in 1 second is considered a valid predictor of therapeutic success.[17] In addition, measurement of the peak expiratory flow rate attainable during a forced expiratory volume with a peak expiratory flow meter may also be used to monitor the status and response of patients to therapy at home and in the office. Furthermore, the observations of decreased dyspnea and improved exercise tolerance following bronchodilator therapy also suggest that such therapy is beneficial.[18]

Some patients whose pulmonary function testing demonstrates a positive response are clinically unresponsive because of improper MDI use. Characteristics that identify such patients include lack of prior instruction and poor knowledge of the correct technique of MDI use.[19]

Anticholinergic Drugs

The inhalation of atropine is avoided in therapy since it is associated with significant systemic side effects owing to a high rate of absorption across the respiratory tract mucosa into the bloodstream.[20,21] Ipratropium, a new synthetic derivative, is poorly absorbed into the circulation and has been shown to have an important role in aerosol therapy and to cause few side effects.[22,23]

The rationale for using anticholinergic agents rests on the knowledge that, in healthy persons, bronchomotor tone is predominantly cholinergically mediated through the parasympathetic nervous system. Atropine and other anticholinergic drugs are parasympatholytic because of their marked affinity for acetylcholine receptor sites on postganglionic parasympathetic nerves, where they act as acetylcholine blockers. The most significant pulmonary parasympathetic outflow occurs through the vagus nerve and is directed to receptors located in the larger airways and submucosal glands, while β-adrenergic drugs exert their greatest effect on small airways. The activity of the vagus nerve is influenced by central stimulation induced by emotional states; consequently, ipratropium is reported to be especially beneficial in those with a strong emotional component in the disease.[24,25]

Anticholinergic agents have a slower onset of action and a longer duration of effect than most β-adrenergic drugs (Table 1). Some report ipratropium to be as effective in treating asthma as the newer β-adrenergic agents; however, the subject remains controversial. The patients with COPD who are most likely to respond to

ipratropium are bronchitic patients and those who fail to respond to a β-adrenergic bronchodilator during pulmonary function testing.[26] Gross has suggested that the optimal response in stable COPD is achieved by using an MDI dose of ipratropium that may be two times the commonly recommended dose of 36 μg.[22] Ipratropium is especially indicated when treating patients with myasthenia gravis whose pulmonary symptoms have worsened because of therapy with cholinesterase inhibitors and patients with asthma who are receiving β-blocking drugs.[22,27]

Ipratropium may cause unexpected bronchospasm.[28,29] Unlike atropine, ipratropium is free of inhibitory effects on mucous secretion and mucociliary transport, has no effect on the urinary sphincter, is less likely than β-adrenergic agonists to cause arterial hypoxemia, and has no effect on intraocular pressure in narrow-angle glaucoma unless sprayed into the eye, or if it is used in combination with albuterol. The ocular side effects can be prevented by using swimming goggles, standing in front of a mirror to observe the path of the inhaled spray, continuing antiglaucoma measures, and using ipratropium and albuterol separately.[22,30]

Glucocorticoid Drugs

The effectiveness of glucocorticoids is attributed to their ability to suppress allergic bronchial inflammation; inhibit intermediate (type 3) hypersensitivity reactions, while having little influence on immediate (type 1) reactions; and restore responsiveness to β-adrenergic drugs. The molecular mechanism of glucocorticoid action proposes steroid diffusion through the cell membrane causing the formation of a messenger RNA and subsequent synthesis of lipocortin, which reduces the release of arachidonic acid, a substrate for prostaglandins and leukotrienes.[6,31]

Based on recent evidence that asthma is a result of a unique type of airway inflammation, Barnes[32] has suggested that "asthma is therefore much more than bronchoconstriction, and treatment must be directed toward reducing this inflammation as well as promoting bronchodilation." Aerosol glucocorticoids used early in the course of asthma improve control of the disease and decrease the need for oral steroids. There have been no well-controlled studies reporting the use of aerosol glucocorticoids in COPD.[33,34]

The potent, longer-acting aerosol glucocorticoids, such as beclomethasone, have a high potency to toxicity ratio. High-dose beclomethasone or budesonide (250 μg per inhalation) is available in Europe, while in the United States the standard inhaler delivers 42 μg per inhalation.[35]

Chronic complicated asthma may require that aerosol glucocorticoid dosages be increased to 16 to 32 inhalations (42 μg per inhalation) daily.[36] A recent review suggests that a four-times-a-day regimen of an aerosol steroid is more effective than a two-times-a-day regimen when using high doses.[37] Side effects are minimal, and the need for oral glucocorticoids is reduced.[35,38]

Adrenal suppression and hypercortisolism are virtually nonexistent when lower doses of the inhaled glucocorticoids are used. One exception, dexamethasone MDI, is associated with a high degree of absorption into the blood and can eventually result in hypercortisolism.[35]

Glucocorticoids are known teratogens. Before they are used by a pregnant woman, the physician should consider the risk-benefit ratio to mother and child. A Food and Drug Administration pregnancy category for prescribing glucocorticoids is not listed.[13]

Biscromones

Aerosolized cromolyn sodium inhibits degeneration of mast cells by antigen and blocks release of the chemical mediators of allergy from sensitized cells. Once the mediators have been released, the drug is rendered ineffective; hence, it is useful in preventing, but not treating, acute paroxysms of asthma after they have developed.

Cromolyn is most effective in treating exercise-induced asthma and should be the first choice in controlling allergic bronchial asthma when an immediate asthmatic response to allergen plays a predominant role.[39]

Cromolyn is available for administration by MDI (800 μg per inhalation) and also as an aerosol powder inhaled from a 20-mg capsule.[40,41] Maximum effect in the treatment of chronic disease is achieved if two inhalations by MDI are taken four times daily and several weeks are allowed for response. Administration 15 to 30 minutes before exercise or exposure to cold dry air or environmental agents effectively prevents the onset of asthma (Table 1).

The powder form of aerosol cromolyn, introduced for use in the United States in 1973, has been associated with serious side effects in a few reported cases.[42–48] Cromolyn, as an MDI aerosol, became available in Europe in 1981 and in the United States in 1986. This formulation seems to be gaining general acceptance with minimal side effects.

Drug Combination Therapy

The clinical presentation of asthma is quite diverse, making it unwise to be too dogmatic with regard to treatment. Obviously, patients should be advised to avoid

Table 2. Therapy Strategies for Mild, Moderate, and Severe Asthma

Mild Asthma	Moderate Asthma	Severe Asthma
1. Aerosol β-adrenergic	1. Increase dose of aerosol β-adrenergic	1. Add systemic steroid
2. Add aerosol cromolyn or aerosol steroid	2. Increase dose of aerosol steroid	
3. Short course of systemic steroid	3. Add theophylline	
	4. Add aerosol anticholinergic	

NOTE: Glucocorticoid lung deposition is improved by using a β-adrenergic agent 5 minutes before administering the glucocorticoid. Adapted from Dolovich and Newhouse.[31]

allergens and occupational sensitizers; sinus disease and esophageal reflux must be treated; and drug-induced asthma due to nonsteroidal anti-inflammatory agents and β-adrenergic antagonists should be eliminated.

A suggested plan for the treatment of mild, moderate, and severe asthma based on present day reports has been outlined in Table 2. It is important to note that an aerosol steroid achieves maximal efficacy and decreases the need for systemic steroid therapy once the acute asthmatic episode has been controlled. During periods of stress or a recurrent asthmatic attack, systemic steroids should be resumed.[13,33]

β-Adrenergic agonists are superior to ipratropium in status asthmaticus, but the combined use of each may result in greater improvement.[22] Exercise-induced asthma is effectively managed by combining ipratropium and cromolyn or a β-adrenergic agonist and cromolyn.[49]

The combination of a β-adrenergic and an anticholinergic agent in COPD provides the rapid onset of action of the former and the sustained activity of the latter with the increased potency of their combined actions. Theophylline potentiates the side effects of β-adrenergic agonists only when they are present in substantial blood levels. Ipratropium can be combined with sympathomimetic and theophylline therapy without any increase in side effects.[50] Theophylline, with a half-life of 7 to 9 hours, is superior in the control of nocturnal asthma. The longer acting β-adrenergic bronchodilators, bitolterol and formoterol (under investigation), show promise for the use in the treatment of this illness.[51–54]

Using the Metered Dose Inhaler

Recommended Procedure

Fifty percent of patients with asthma and 62% of adult outpatients with COPD use the MDI incorrectly.[19] It has been shown, however, that following a single instruction in correct use, 77% to 80% demonstrate the correct technique for using the inhaler. Additional verbal instruction, followed by a time during which the patient practices proper use of the inhaler, improves patient performance.[55,56]

Recent authoritative research suggests that the MDI should be administered by the open-mouth method of Newhouse and Dolovich[10] (Table 3). This technique is considerably more effective than the closed-mouth method recommended by drug manufacturers. Using radioactively labeled MDI-generated aerosols, the open-mouth method has been demonstrated to deliver twice as much medication to the lower respiratory tract with significantly improved bronchodilation.[57]

The rationale for the open-mouth technique is that about 80% of an MDI aerosol dose deposits in the oropharynx and only 10% reaches the lung. The particle size of the therapeutic aerosols generated varies from 0.5 μm to 35 μm, but only the particles between 1 μm and 5 μm are deposited in the lower respiratory tract. The deposition of these particles depends on impaction, sedimentation, and diffusion. Impaction causes particles greater than 5 μm to deposit in the upper airways; this effect increases at high inspiratory flow rates. Particles 1 to 5 μm in size are deposited in the small airways by sedimentation (a gravitational effect), where the main therapeutic effect is achieved. Their deposition is increased by slow inspiratory flow rates (less than 1 L/sec) and a 4- to 10-second period of breath-holding, which allows time for sedimentation. The therapeutic value of

Table 3. Open-Mouth Method of Using the Metered Dose Inhaler

Personnel supervising treatment should instruct patients in the recommended open-mouth procedure as follows:

1. Shake the metered dose inhaler three or four times.
2. Hold the mouthpiece 4 cm in front of the widely opened mouth.
3. Exhale to resting end expiration (end tidal volume).
4. Actuate the inhaler and slowly inhale for 5 seconds to total lung capacity.
5. Hold breath at total lung capacity for as long as possible or up to 10 seconds.
6. Slowly exhale.

Adapted from Newhouse and Dolovich.[10]

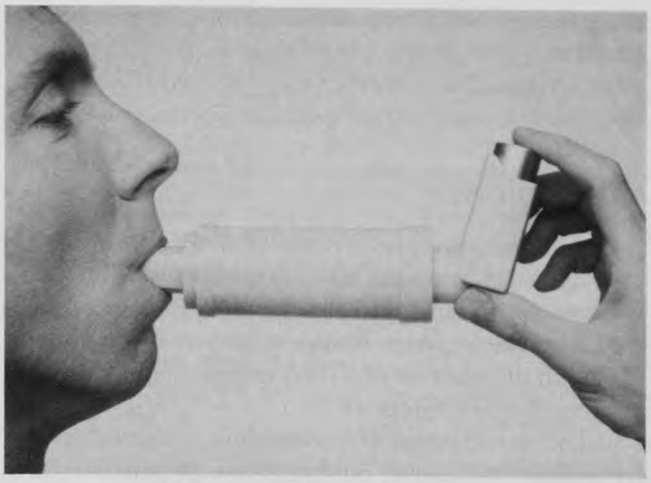

Figure 1. Demonstration of a patient using a spacer (AeroChamber) attached to a metered dose inhaler. (Photograph courtesy of Forest Pharmaceuticals, Inc.)

particles less than 0.1 μm in size, the movement of which is controlled by diffusion, has not been clearly defined.[10,58]

The most common patient errors encountered are inability to coordinate firing the aerosol with inhalation, to inhale slowly, and to hold a breath adequately.[57,58] Prewarming the MDI canister to body temperature when atmospheric temperatures are low increases the lower airway deposition from 17% to 32% as the temperature rises from 4°C to 32°C (39.2°F to 89.6°F).[59]

The mouthpiece of the MDI canister should be inspected before use to prevent accidental inhalation of foreign bodies lodged in the mouthpiece (mouthpiece caps, coins, capsules).[60]

Spacers and Delivery Systems

Spacers are extensions in the form of a tube that serve as a holding chamber for the drug released from the MDI canister and from which the patient can more easily inhale the medication (Figure 1). These devices overcome a patient's lack of hand-lung coordination, decrease oropharyngeal deposition, and improve lung deposition by enhancing propellant vaporization, which results in more respirable particles.[10,61,62] The MDI releases the aerosol into the chamber, and the patient inhales as described in Table 4. Children may simply put the chamber in the mouth and breathe normally for 20 to 30 seconds, after which the MDI aerosol is released into the chamber, and normal breathing is continued for 3 or 4 more breaths.

A significant number of patients are unable to properly use an MDI because of: severe asthma with an inability to inhale slowly and hold a breath; arthritis and stroke with poor hand-breath coordination; or age, eg, children under 5 years. It is in such patients that a spacer will enhance the use of the MDI. Spacers also decrease the side effects of inhaled glucocorticoids, namely, systemic effects sometimes seen with high dosages, and the occurrence of thrush, reported in 5% to 15% of patients.[63,64]

Table 4. Using a Spacer with the Metered Dose Inhaler

1. Insert the inhaler mouthpiece into the chamber.
2. Shake the inhaler a few times.
3. Place the chamber mouthpiece in the mouth and close the lips.
4. Exhale to resting end expiration (end tidal volume).
5. Spray one puff from the inhaler into the chamber.
6. Inhale for 5 seconds to total lung capacity.
7. Hold breath at total lung capacity for as long as possible, up to 10 seconds.
8. Slowly exhale.

Adapted from Physicians' Desk Reference.[13]

Recently, manufacturers have attempted to improve the performance of the MDI by developing powder inhalers that do not require hand-lung coordination for inhalation. These powder devices have not shown any better patient acceptance or therapeutic benefit than the MDI aerosol unit.[40,41,65,66]

Replacement of the Jet Nebulizer by the MDI

Current studies demonstrate that the MDI is as effective as the jet nebulizer when used to treat moderate and severe airflow obstruction in both hospital and outpatient settings.[67–70]

Replacement of the jet nebulizer with the MDI in hospitals has the potential to contribute to more cost-effective medical care. Jasper et al[71] state that self-administration of a bronchodilator by MDI in all adult patients not in an intensive care setting would save $253,487 per year in their institution alone. Summer et al[72] report a study in which the use of the jet nebulizer resulted in patient charges of $4159 and respiratory therapist time of 3808 minutes; comparative values for the MDI were $1024 and 840 minutes, respectively.

The MDI can be used to administer the whole range of available aerosol medications and has the additional attributes of simplicity, portability, and protection of medications from contamination. Also, an MDI may be used to successfully treat severe asthma in the emergency department. Although previously the standard method of care, administration of aerosols by intermittent positive pressure breathing remains useful only in the treatment of croup with epinephrine and laryngeal candidiasis with

nystatin since high inspiratory flow rates are needed to increase delivery of these drugs to the larynx.[73,74]

Mechanical Ventilation and the MDI

Intubated patients can effectively receive aerosol medications through the endotracheal tube.[75] The MDI is more efficient and interferes less with the patient's respiration than the jet nebulizer in treating ventilator patients.[76–78] The efficient use of the MDI with a mechanical ventilator depends on a slow flow, a deep inspiration, and a sustained peak inspiratory pause delivered by the ventilator or in using bag-assisted ventilation. The use of bronchodilating agents in this manner serves to decrease the work of breathing, lessens patient dyspnea, and reduces weaning time.[79]

Concerns About Asthma Mortality and Drug Toxicity

Despite the clinical reports of the effectiveness of using higher dosages of aerosol drugs, the drug manufacturers have not offered any official comment or ordered any sanction to increase recommended dosage levels.

There is an ongoing concern about the potential cardiac effects of inhaled β-adrenergic drugs and fluorocarbon propellants.

Evaluations of propellant toxicity have led to the speculation that humans would have to use an inhaler 20 times over a period of 2 minutes without exhaling before myocardial fluorocarbon concentrations become critical. The Asthma Mortality Task Force concluded that "the role of cardiac pathology in death from asthma remains uncertain," and that "the clinical importance of the arrhythmogenic potential of bronchodilator drugs (and combinations thereof) used in the acute and chronic treatment of asthma remains unresolved."[80]

Overall, the Task Force concluded in 1987 that "there are no experimental data to show that any of the drugs used to treat asthma are responsible for the increases in deaths reported in various parts of the world"; however, some asthma medications do have toxic potential, and "deaths are still reported in circumstances that suggest treatment has proved inadequate."[81]

The topic has been refueled by a recent report that a pharmaceutical company wrote a confidential letter to the Food and Drug Administration alerting it to a Canadian study reporting that asthma patients using twice the recommended daily dosage of β-adrenergic drugs faced double the risk of a fatal or near-fatal asthma attack.[82] The report must be viewed with caution since other factors should be considered; for example, patients taking the greatest amount of drug might also have the most severe asthma. Further study is needed.

Conclusions

Asthmatic patients who are free of disease for extended periods usually respond to a β-adrenergic MDI when symptoms arise, and persistent symptomatology requires a prophylactic regimen including an aerosol glucocorticoid with the addition of a β-adrenergic, anticholinergic, or cromolyn as appropriate.

The newer aerosol β-adrenergic drugs (albuterol, terbutaline, pirbuterol, bitolterol) are β_2 selective, producing bronchodilation with less cardiac stimulation than the older β-adrenergic drugs (epinephrine, isoproterenol, isoetharine, mataproterenol). The longer acting β-adrenergic bronchodilators bitolterol and formoterol (investigational) may prove to be helpful in treating nocturnal asthma. Aerosol β-adrenergic drugs have value in replacing oral theophylline as first-line therapy since they are more potent bronchodilators and considerably less toxic.

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