



DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington DC 20420

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SPECIAL COUNSEL

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In Reply Refer To:

Scott J. Bloch
U.S. Office of Special Counsel
1730 M Street, N.W. Suite 300
Washington, DC 20036-4505

Dear Mr. Bloch:

The Department of Veterans Affairs' Office of General Counsel notified me of an informal contact between your staff and their office asking that the report VA submitted on November 18, 2005, in response to Office of Special Counsel File Number DI-05-180, be revised to include documentation of an interview with the complainant. As a result of that request, the Office of the Medical Inspector (OMI) conducted such an interview. The complainant's viewpoint is provided in the attached revised report. The OMI conclusions are unchanged and all of the complainant's allegations remain unsubstantiated.

If you have any questions about the content of the report, please have a member of you staff contact Mr. Terry A. Morrow, CHE, Director, Operations and Administration, Management Support Office, on 202-273-9282.

Sincerely yours,


Nevin M. Weaver, FACHE
Chief Management Support Officer

Enclosure

Date

U.S. OFFICE OF SPECIAL COUNSEL
1730 M. Street, N. W. Suite 300
Washington, DC 20036-4505

Re: OSC File N. DI-05-1801

Dear Mr. Bloch:

Introduction

The Office of the Medical Inspector (OMI) was asked by the Principal Deputy Under Secretary for Health to review the clinical issues related to a complaint lodged with the Office of Special Counsel (OSC) by a respiratory therapist employed at the VA Medical Center, Miami, FL (the Medical Center) regarding events that took place between March 6, 2005 and May 13, 2005. The complainant alleges that patients with pulmonary disease were not receiving proper treatment at the Medical Center. More specifically, the complainant alleges:

1. In order to cut costs, the Medical Center management instructed medical personnel to incorrectly administer dosages of two medications, albuterol sulfate and ipratropium bromide, via nebulizer to patients receiving respiratory treatments. The complainant advised the OSC that albuterol sulfate comes in packages containing 2.5 milligrams (mg) of albuterol in 3.0 cubic centimeters (cc) of saline solution and ipratropium bromide comes in packages containing 0.5 mg of ipratropium bromide in 3.0 cc of saline solution; and that management has instructed the medical staff to mix the albuterol sulfate and ipratropium bromide packages together in order to administer them at the same time. The complainant alleges that this procedure has the effect of reducing the efficacy of each drug by approximately one-half, as it doubles the amount of saline solution.
2. Management instructs medical personnel to administer these drugs at incorrect time intervals.
3. Management directs medical personnel to falsely claim on a patient's medical record that the medication was administered at correct intervals.
4. The OMI spoke with the complainant on January 20, 2006. He repeated the assertions he had made to the OSC and he added a new one. He said the nebulizers used to deliver the combination of albuterol and ipratropium mixture are made to hold 4 cc of fluid not 6 cc, the total volume of albuterol and ipratropium bromide when combined. He made an additional statement that there is a preparation of albuterol that comes in 2.5 mg per 0.5 cc; when mixed with ipratropium at 0.5 mg in 3.0 cc, this combination makes a total volume 3.5 cc not 6 cc. He said that this smaller volume is preferable to the 6 cc mixture used by the Medical Center.

Facility Profile

The Miami VA Medical Center and its attached four-story nursing home are located on a 26.3 acre campus. The Medical Center opened in 1968 and provides general medical, surgical, and psychiatric services; it also serves as an AIDS-/HIV Center, a Prosthetic Treatment Center, Spinal Cord Injury Rehabilitative Center, and Geriatric Research Education and Clinical Center. The facility is recognized as a Center of Excellence in Spinal Cord Injury Research and Substance Abuse Treatment.

The Medical Center operates a 285-bed tertiary care teaching hospital and a 144-bed nursing home care unit. A full range of inpatient, including open heart surgery, and outpatient care is provided, including beds in medicine (82), surgery (30), intermediate care (36), neurology (5), psychiatric rehabilitation (58), psychiatry (32), rehabilitation medicine (6), and spinal cord (36). The Medical Center is also responsible for two major Satellite Outpatient Clinics, two Readjustment Counseling Centers, and several Community Based Outpatient Clinics.

The Medical Center has several affiliations but its primary affiliation is with the University Of Miami School Of Medicine. It has research programs in diseases affecting bones and joints, prostate disorders, mental health, HIV, dental health and is conducting special studies in infectious diseases, neurological disorders, and renal diseases. Residency training programs are provided to 150 residents in most of the medical and surgical subspecialties, as well as in pathology, psychiatry, and radiology. Other training programs exist in nursing, audiology/speech pathology, pharmacy, social work, nutrition and food service, nuclear medicine, radiology, and physical and occupational therapy.

Methods for Conducting the Investigation

The OMI contacted the Medical Center to notify the Director of the complaint and of the OMI's plan to conduct a site visit. The site visit took place October 3 – 5, 2005, with the Medical Center staff providing full cooperation. The OMI team consisted of the OMI's Chief of the Clinical Investigation Division (a registered nurse) from VA Central Office, a Chief of Pulmonary Critical Care and Occupational Medicine (a physician) and a Chief Respiratory Therapist, the latter two both from another VA medical center. The team toured units where a large number of respiratory nebulizer treatments are performed: the medical intensive care unit (MICU), and two medical wards. The team spoke briefly with three patients about their satisfaction with their respiratory treatments; observed the administration of two nebulizer treatments and one metered dose inhaler; assessed the equipment used in the administration of treatments; and observed the documentation of treatments provided. The team also reviewed the policy related to the administration of the medications in respiratory therapy treatments and conducted interviews with 32 Medical Center staff and reviewed 42 individual electronic medical records of patients treated during the time frame of the complaint.

The OMI team interviewed the following leadership and clinical staff: Director; Chief of Staff; Associate Director; Chief Nurse; Chief, Quality Management; Risk Manager;

Patient Advocate; Chief, Human Resources; Compliance Officer; Chief, Respiratory Therapy; Chief Medical Resident; Chief, Pulmonary Care; Administrative Officer of the Medicine Service; and a respiratory therapy (RT) evaluator. There were four group interviews: one with three night shift RTs; another with two day shift RTs and two evening shift RTs; another with pharmacy personnel including the Chief, Pharmacy Service, three pharmacy staff and two pharmacy technicians; and a final group of five staff nurses.

It should be noted that on May 4, 2005, the complainant contacted the Inspector General's (IG) Hotline and expressed similar concerns about the delivery of respiratory care at the Medical Center. The Hotline Division forwarded the case (Hotline Case Number 2005 02199-HL-0588) to the Office of Healthcare Inspections (OHI) who investigated the case. Following an Administrative Investigative (AI) conducted by the Medical Center in June 2005, OHI found no improprieties related to the administration of the two medications; however, areas needing improvement were identified:

a) improve consistent documentation of respiratory treatments, b) improve staffing of the respiratory unit, c) improve recruitment and retention strategies for respiratory therapists, and d) clarify policy on the administration of medications via aerosol delivery devices.

Findings

a.) Respiratory Care Unit (RCU)

The Respiratory Care Unit (RCU) is under the direction of the Chief, Medical Service with 22 full time equivalent employees (FTEEs) and two vacancies. There is a Chief RT, an Assistant Chief (who runs the blood gas laboratory), and two RT evaluators (one on day shift and one on night shift).

The Medical Center has had problems recruiting and retaining RTs; most of the staff interviewed attributed this to non-competitive salaries. The RCU had 3.6 FTEEs that remained vacant for an extended period of time. In a facility-wide initiative to reduce cost, the Medical Service reduced RCU's FTEEs by permanently eliminating the 3.6 FTEEs, which, in the opinion of many of the staff interviewed, leaves the RCU short of staff.

b.) RCU Policy

The RTs are responsible for the administration of the medications albuterol sulfate and ipratropium bromide. Albuterol sulfate is a beta2-adrenergic short-acting bronchodilator which has been shown to have positive effects in the form of bronchial smooth muscle relaxation. It is indicated for the relief of bronchospasm in patients two years of age and over with reversible obstructive airway disease and acute attacks of bronchospasm. The albuterol sulfate preparation currently used by VHA comes in a 2.5 mg dose in 3.0 cc of saline solution. Ipratropium bromide is a long-acting, inhaled anticholinergic bronchodilator that is administered either alone or with other bronchodilators, especially beta adrenergics. It is indicated for maintenance treatment of bronchospasm associated

with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Ipratropium bromide comes in a package containing 0.5 mg in 3.0 cc of saline solution

The AI conducted in June 2005 found that the Medical Center policy, *Selection of Aerosol Delivery Device Code, 7.0* discussed the administration of medications by drug class and did not address the specific medications administered by the RTs. As noted above, the OHI also identified that the policy needed to be clarified. At the time of the OMI visit, a new policy had been drafted and was in the concurrence process which identified how albuterol sulfate and ipratropium bromide are to be mixed when ordered.

c.) Staff Interviews

Medical Center leadership (Director, Chief of Staff Associate Director, and Nurse Executive) all support the use of overtime to cover staffing shortages in the RCU to meet patient care needs. In addition, leadership said that the cost of each of the two medications in question is minimal and would not be targeted in an effort to cut costs. When asked directly, each denied instructing medical personnel to administer albuterol sulfate and ipratropium bromide at incorrect intervals and to document that they were given falsely as ordered.

The Compliance Officer provides education to the entire facility staff about reporting unethical or fraudulent behavior at periodic training and in new employee orientation. The Compliance Officer developed a matrix reporting structure for employees, patients, and family members. Exit interviews with staff leaving the Medical Center are also conducted. At the complainant's exit interview, concerns were reported regarding the administration of respiratory treatments. In addition, the Compliance Officer instructed the complainant on how to report his concerns, which he did. The Compliance Officer has no independent knowledge of unethical behavior relating to the three allegations lodged by the complainant.

The Chief, Pulmonary Medicine and the Chief Medical Resident had no knowledge of any unethical behavior related to the allegation lodged by the complainant, nor did they instruct anyone to carry out the acts described by the complainant. They both agreed that the RCU is short of staff and that the RTs do a good job caring for patients.

Nurses from the medical wards, the MICU, and nursing home were interviewed. They also believe that the RCU is short of staff, and on occasion the nurses will start the treatments when the RTs are busy. They acknowledge that it would be difficult to give every treatment as prescribed with the current number of RTs and with all of the unit activities. The nurses provide the nebulizer treatment in the nursing home with support from the RCU when needed. A senior RT provides annual competency reviews for the nursing home staff as well as training and education during new employee orientation for clinical staff.

Pharmacy staff expressed that mixing albuterol sulfate and ipratropium bromide in a nebulizer is the appropriate way to administer these medications and that this practice has been long standing and preferred. They identified no contraindications to this mixing. The cost of the two drugs is described as “pennies” and does not have a significant budgetary impact. They too asserted that the cost of these medications is minute and did not support the allegations of the complainant.

The Chief, RCU indicated that when an order is written for respiratory treatment, a request prints out in the RCU office; however, since there is no administrative support in the office, the order may sit until a RT returns to the unit. Once an order is received, an RT evaluator will evaluate the patient and review the order. If there are concerns about either, the evaluator will contact the prescribing physician for clarification. If no concerns are identified, the treatments will be initiated. The Chief believes the RT staff to be professional, well trained, and dedicated to providing quality care to veterans. Some barriers to completing all ordered therapies or documenting all therapies provided are the large workload carried by each RT, charting treatments in as many as four places, and having to wait for a computer to document treatments. The Chief, RCU denies asking her staff to falsify medical records by charting treatments that were not given or advising staff to give treatments at less frequent intervals.

The RTs interviewed denied that anyone told or asked them to falsify medical records or give respiratory treatments at less frequent intervals to save money or for any other reason. The RTs said that they would not do this because it would be a risk to their licenses and professional careers. They do admit that they do the best they can, given the staffing shortage of RTs and high volume of treatments ordered. If they are unable to get to a treatment they pass it on to the next shift.

d. Observations

The OMI team observed the administration of two nebulizer treatments. The two medications, albuterol sulfate and ipratropium bromide, were obtained from the Pyxis or medication cart, poured into a small-volume nebulizer as 5-6 cc of liquid in a 10 cc chamber, and administered by face mask. The RTs appropriately identified the patient, explained the treatment, assessed the patient, took vital signs (before and after), and provided patient education. The treatment took approximately 13 minutes to administer. The RTs use a work log to document treatments provided, which are later transcribed into the electronic medical record on a template especially designed for RT treatments. There was no evidence of failure, non-availability, or shortages of any equipment.

e. Medical Record Review

During the period in question, March 6, 2005 to May 13, 2005, 154 patients were ordered albuterol sulfate and ipratropium bromide to be given as a mixture. A review of 42 of the 154 patient’s electronic medical records revealed that when RT treatments are ordered to be given “now” they were generally not given in a timely fashion, few patients received all of the treatments ordered, and there was inconsistent documentation as to when or

why treatments were missed. If allegation #3 is true (falsification of records), the review would have revealed more consistent documentation and fewer missed treatments. In sum, the medical record review does not support the claim that staff falsely documented that treatments were given at the correct interval when they were not.

It was clear to the OMI team that several factors contribute to patients not receiving all of their treatments: patients are often out of their rooms for tests or other reasons, a patient emergency that requires and diverts the full attention of the RT, and the staffing shortage in the RCU.

The Quality Manager, Risk Manager, and the Patient Advocate denied having any knowledge of unethical behavior on behalf of the hospital leadership in this regard. Each was asked to review their records for the period of the complainant's employment to determine if there were any specific complaints about respiratory care; adverse events resulting in root cause analyses (RCAs) being conducted about respiratory care; or peer review or other quality measures that identified issues with the quality of respiratory care provided. None were reported.

Summary of the Evidence

As mentioned in the introductory paragraph of this communication, the complainant stated that the "management" had incorrectly requested that medical personnel mix the albuterol and the ipratropium bromide prior to administering it by inhalation to patients. He stated that such mixing was endangering the health of the veterans so-treated, because it was diluting the medications, causing them extreme discomfort and at heightened risk for cardiac arrest. It is important to note the inaccuracy of these allegations. These two medications, both used for treatment of bronchospasm in individuals with obstructive lung disease and/or asthma, are very frequently used as a mixed combination. In fact, the FDA-approved labeling for ipratropium bromide states "ipratropium bromide inhalation solution has been shown to be a safe and effective bronchodilator when used in conjunction with beta adrenergic bronchodilators." (see attachments A & B). Additionally, it is relevant to note that there is a fixed combination aerosol, with the trade name Combivent®, which contains both ipratropium bromide and albuterol. In regard to the question of dilution, it should be noted that any aerosol solution used for inhalation treatments is to be inhaled until the vial is empty. The pharmacologic effects are dependent upon the amount of the medication, not its dilution. When an inhaled medication is used, there is always a tiny residual amount (called the "dead volume") which may be left in the inhalation system. This residual, in terms of amount of drug, will actually be less if the medications are in a larger volume (see Hess, D, Fisher, D., Williams, P, Pooler, S. and Kacmarek, RM, *Medication nebulizer performance. Effects of diluent volume, nebulizer flow, and nebulizer brand.* 1996, Chest:Aug;110(2):498-505). So there may be more complete delivery in a larger volume of the same mg. dose; than in a smaller volume.

The OMI consulted with the Pharmacy Benefits Management Office and learned that VHA's prime pharmacy vendor (McKesson) as well as VHA's formulary both offer albuterol sulfate and that VHA Medical Centers have traditionally used the 2.5 mg in 3 cc

of saline preparation. In addition, the packaging of albuterol and ipratropium comes in a variety of ways, including a pre-mixed unit dose of the two drugs. The most critical factor in the delivery of these medications, regardless of the concentration, is that the patient receives their full dose of medication.

VHA's Clinical Practice Guideline for the Management of Persons with Chronic Obstructive Pulmonary Disease or Asthma (Version 1.0, November 17, 1997) clearly supports the mixing of these two medications as a more affective way of managing bronchospasm (Attachment C).

Conclusions

Allegation # 1: *OMI Conclusion: The medications come packaged as described by the complainant; however, mixing albuterol sulfate and ipratropium bromide in the treatment of bronchospasm is a long standing policy and is supported by the manufacturer's recommendations. VHA Clinical Practice Guideline for the Management of Person with Chronic Obstructive Pulmonary Disease or Asthma also supports this technique. The cost of these medications is minimal and there would be no cost savings advantage to mixing them.*

Allegation #2: *OMI Conclusion: The OMI found no evidence that management, at any level, instructed medical personnel to administer these medications at incorrect intervals.*

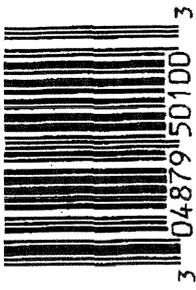
Allegation #3: *OMI Conclusion: The OMI found no evidence that management, at any level, instructed medical personnel to falsely claim on a patient's medical record that they gave the patient the medication at the correct intervals.*

Allegation #4: *OMI Conclusion: The OMI found that the nebulizer used by the Medical Center during the time the complainant was employed is made to hold up to 10 cc of liquid. In addition, no contraindications were found regarding the use of albuterol 2.5 mg in 3 cc of saline as currently employed by the Medical Center.*

In summary, the OMI found that mixing albuterol sulfate and ipratropium bromide is standard practice and does not represent a threat to veterans' health. No violation of clinical practice or apparent violation of any law, rule, or regulation was found. However, The OMI agrees with the findings of the OIG-OHI investigation and recommends that the Medical Center:

- 1.) Improve documentation by the RTs
- 2.) Fully staff the RCU
- 3.) Improve recruitment and retention strategies for RTs.

An action plan will be forthcoming from the Medical Center.

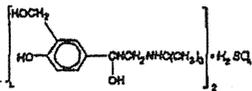


ATTACHMENT A

Albuterol Sulfate Inhalation Solution, 0.083%*

*Potency expressed as albuterol.
DESCRIPTION

Albuterol Sulfate Inhalation Solution is a relatively selective beta₂-adrenergic bronchodilator (see CLINICAL PHARMACOLOGY). Albuterol sulfate, USP, is the racemic form of albuterol, has the chemical name 2'-[(tert-Butylamino)methyl]-4-hydroxy-m-xylene-α,α'-diol sulfate (2:1) (salt) and the following structural formula:



Albuterol sulfate has a molecular weight of 576.71, and the molecular formula is (C₂₁H₂₇NO₆)₂ • H₂SO₄. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

Albuterol Sulfate Inhalation Solution requires no dilution before administration by nebulization.

Each milliliter of Albuterol Sulfate Inhalation Solution contains 0.83 mg of albuterol (as 1 mg of albuterol sulfate) in an isotonic, sterile, aqueous solution containing sodium chloride; sulfuric acid is used to adjust the pH to between 3 and 5. Albuterol Sulfate Inhalation Solution contains no soothing agents or preservatives.

Albuterol Sulfate Inhalation Solution is a clear, colorless to light yellow solution.

CLINICAL PHARMACOLOGY

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta₂-adrenergic receptors compared with isoproterenol. While it is recognized that beta₂-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that 10% to 60% of the beta-receptors in the human heart may be beta₂-receptors. The precise function of these receptors has not been established.

The pharmacologic effects of beta₂-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta₂-adrenergic receptors of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects.

Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta₂-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-O-methyl transferase.

Pharmacokinetics: Studies in asthmatic patients have shown that less than 20% of a single albuterol dose was absorbed following either IPPB (intermittent positive-pressure breathing) or nebulizer administration; the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. Following a 3-mg dose of nebulized albuterol in adults, the maximum albuterol plasma levels at 0.5 hours were 2.1 ng/mL (range, 1.4 to 3.2 ng/mL). There was a significant dose-related response in FEV₁ (forced expiratory volume in one second) and peak flow rate. It has been demonstrated that following oral administration of 4 mg of albuterol, the elimination half-life was 5 to 6 hours.

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minkigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

Clinical Trials: In controlled clinical trials in adults, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by FEV₁. FEV₁ measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in FEV₁ over baseline values) continued for 3 to 4 hours in most patients, with some patients continuing up to 6 hours.

Within 2 to 20 minutes following single doses of albuterol inhalation solution. An increase of 15% or more in baseline FEV₁ has been observed in children aged 5 to 11 years up to 6 hours after treatment with doses of 0.10 mg/kg or higher of albuterol inhalation solution. Single doses of 3, 4, or 10 mg resulted in improvement in baseline PEFR that was comparable in extent and duration to a 2-mg dose, but doses above 3 mg were associated with heart rate increases of more than 10%.

INDICATIONS AND USAGE

Albuterol Sulfate Inhalation Solution is indicated for the relief of bronchospasm in patients 2 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.

CONTRAINDICATIONS

Albuterol Sulfate Inhalation Solution is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

WARNINGS

Paradoxical Bronchospasm: Albuterol Sulfate Inhalation Solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Albuterol Sulfate Inhalation Solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

Cardiovascular Effects: Albuterol Sulfate Inhalation Solution, like all other beta₂-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Albuterol Sulfate Inhalation Solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta₂-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Albuterol Sulfate Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Albuterol Sulfate Inhalation Solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

Use of Anti-inflammatory Agents: The use of beta₂-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids.

PRECAUTIONS

General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta₂-adrenergic bronchodilator.

Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Repeated dosing with 0.15 mg/kg of albuterol inhalation solution in children aged 5 to 17 years who were initially normokalemic has been associated with an asymptomatic decline of 20% to 25% in serum potassium levels.

Information For Patients: The action of Albuterol Sulfate Inhalation Solution may last up to 6 hours or longer. Albuterol Sulfate Inhalation Solution should not be used more frequently than recommended. Do not increase the dose or frequency of Albuterol Sulfate Inhalation Solution without consulting your physician. If you find that treatment with Albuterol Sulfate Inhalation Solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using Albuterol Sulfate Inhalation Solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, and tremor or nervousness. If you are pregnant or nursing, contact your physician about use of Albuterol Sulfate Inhalation Solution. Effective and safe use of Albuterol Sulfate Inhalation Solution includes an understanding of the way that it should be administered.

Drug compatibility (physical and chemical), efficacy, and safety of Albuterol Sulfate Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

See Illustrated Patient's Instructions for Use.

Drug Interactions: Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta-Blockers: Beta₂-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Albuterol Sulfate Inhalation Solution, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta₂-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Patient's Instructions for Use

Albuterol Sulfate Inhalation Solution, 0.083% *Potency expressed as albuterol

Read complete instructions carefully before using.

1. Twist open the top of one Albuterol Sulfate Inhalation Solution unit-of-use container and squeeze the entire contents into the nebulizer reservoir (Figure 1).



Figure 1

2. Connect the nebulizer reservoir to the mouthpiece or face mask (Figure 2).

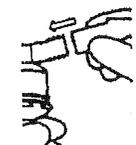


Figure 2

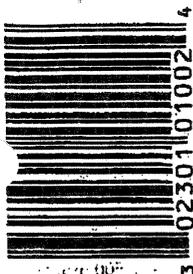
3. Connect the nebulizer to the compressor.
4. Sit in a comfortable, upright position; place mouthpiece in your mouth (Figure 3) or the face mask; and turn on the compressor.



Figure 3

5. Breathe as calmly, deeply and evenly possible until no more mist is formed in nebulizer chamber (about 5 to 15 minutes at this point, the treatment is finished).
6. Clean the nebulizer (see manufacturer's instructions).

(continued on other side)

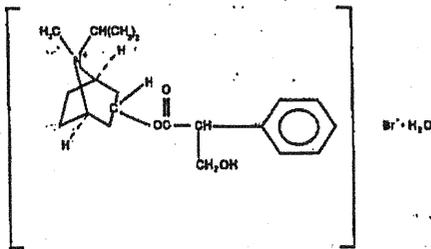


ATTACHMENT B

Rx only

Prescribing information

DESCRIPTION The active ingredient in Ipratropium bromide inhalation solution is ipratropium bromide monohydrate. It is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (endo, syn)-(+); a synthetic quaternary ammonium compound, chemically related to atropine.



Ipratropium bromide monohydrate

C22H38BrNO3.H2O Mol. Wt. 430.4

Ipratropium bromide is a white crystalline substance, freely soluble in water and lower alcohols. It is a quaternary ammonium compound and thus exists in an ionized state in aqueous solutions. It is relatively insoluble in non-polar media.

Ipratropium bromide inhalation solution is administered by oral inhalation with the aid of a nebulizer. It contains ipratropium bromide 0.02% (anhydrous basis) in a sterile, preservative-free, isotonic saline solution, pH-adjusted to 3.4 (3 to 4) with hydrochloric acid.

CLINICAL PHARMACOLOGY Ipratropium bromide is an anticholinergic (parasympatholytic) agent that, based on animal studies, appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increases in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) that are caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.

The bronchodilation following inhalation of ipratropium bromide inhalation solution is primarily a local, site-specific effect, not a systemic one. Much of an administered dose is swallowed but not absorbed, as shown by fecal excretion studies. Following nebulization of a 2 mg dose, a mean of 7% of the dose was absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract. The half-life of elimination is about 1.6 hours after intravenous administration. Ipratropium bromide is minimally (0 to 9% in vitro) bound to plasma albumin and alpha1-acid glycoproteins. It is partially metabolized. Autoradiographic studies in rats have shown that ipratropium bromide inhalation solution does not penetrate the blood-brain barrier. Ipratropium bromide inhalation solution has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in those patient populations.

In controlled 12-week studies in patients with bronchoapasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV1 increases of 15% or more) occurred within 15 to 30 minutes, reached a peak in 1-2 hours, and persisted for periods of 4-5 hours in the majority of patients, with about 25-38% of the patients demonstrating increases of 15% or more for at least 7-8 hours. Continued effectiveness of ipratropium bromide inhalation solution was demonstrated throughout the 12-week period. In addition, significant increases in forced vital capacity (FVC) have been demonstrated. However, ipratropium

bromide inhalation solution did not consistently produce significant improvement in subjective symptom scores nor in quality of life scores over the 12-week duration of study. Additional controlled 12-week studies were conducted to evaluate the safety and effectiveness of ipratropium bromide inhalation solution administered concomitantly with the beta adrenergic bronchodilator solutions metaproterenol and albuterol compared with the administration of each of the beta agonists alone. Combined therapy produced significant additional improvement in FEV1 and FVC. On combined therapy, the median duration of 15% improvement in FEV1 was 5-7 hours, compared with 3-4 hours in patients receiving a beta agonist alone.

INDICATIONS AND USAGE Ipratropium bromide inhalation solution administered either alone or with other bronchodilators, especially beta adrenergics, is indicated as a bronchodilator for maintenance treatment of bronchoapasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

CONTRAINDICATIONS Ipratropium bromide inhalation solution is contraindicated in known or suspected cases of hypersensitivity to ipratropium bromide, or to atropine and its derivatives.

WARNINGS The use of ipratropium bromide inhalation solution as a single agent for the relief of bronchoapasm in acute COPD exacerbation has not been adequately studied. Drugs with faster onset of action may be preferable as initial therapy in this situation. Combination of ipratropium bromide inhalation solution and beta agonists has not been shown to be more effective than either drug alone in reversing the bronchoapasm associated with acute COPD exacerbation. Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchoapasm and oropharyngeal edema.

PRECAUTIONS General: Ipratropium bromide inhalation solution should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy or bladder neck obstruction.

Information For Patients: Patients should be advised that temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma or eye pain may result if the solution comes into direct contact with the eyes. Use of a nebulizer with a mouthpiece rather than a face mask may be preferable, to reduce the likelihood of the nebulizer solution reaching the eyes. Patients should be advised that ipratropium bromide inhalation solution can be mixed in the nebulizer with albuterol or metaproterenol if used within one hour. Drug stability and safety of ipratropium bromide inhalation solution when mixed with other drugs in a nebulizer have not been established. Patients should be reminded that ipratropium bromide inhalation solution should be used consistently as prescribed throughout the course of therapy.

Drug Interactions: Ipratropium bromide inhalation solution has been shown to be a safe and effective bronchodilator when used in conjunction with beta adrenergic bronchodilators. Ipratropium bromide inhalation solution has also been used with other pulmonary medications, including methylxanthines and corticosteroids, without adverse drug interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic potential at dietary doses up to 6 mg/kg/day of ipratropium bromide.

Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg/day was unaffected by ipratropium bromide inhalation solution administration. At doses above 90 mg/kg, increased resorption and decreased conception rates were observed.

Pregnancy TERATOGENIC EFFECTS

Pregnancy Category B. Oral reproduction studies performed in mice, rats and rabbits at doses of 10, 100 and 125 mg/kg respectively, and inhalation reproduction studies in rats and rabbits at doses of 1.5 and 1.8 mg/kg (or approximately 38 and 45 times the recommended human daily dose) respectively, have demonstrated no evidence of teratogenic effects as a result of ipratropium bromide inhalation solution. However, no adequate or well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, ipratropium bromide inhalation solution should be used during pregnancy only if clearly needed.

Patient's Instructions for Use

Ipratropium Bromide Inhalation Solution, 0.02%

Read complete instructions carefully before using.

- 1. Twist open the top of one unit dose vial and squeeze the contents into the nebulizer reservoir (Figure 1).

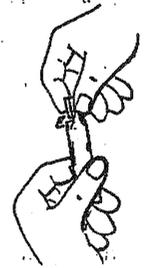


Figure 1

- 2. Connect the nebulizer reservoir to the mouthpiece or face mask (Figure 2).

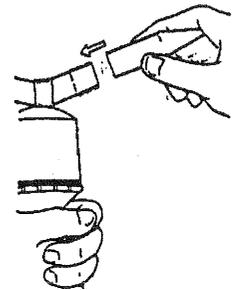


Figure 2

- 3. Connect the nebulizer to the compressor.

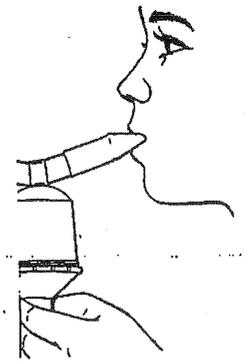


Figure 3

- 4. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 3) or put a face mask and turn on the compressor. If a mask is used, care should be taken to avoid leakage around the mask as temporary blur vision, precipitation or worsening of narrow-angle glaucoma, or eye pain may occur if the solution comes into direct contact with the eyes.

**VETERANS HEALTH ADMINISTRATION
CLINICAL PRACTICE GUIDELINE FOR THE
MANAGEMENT OF PERSONS WITH CHRONIC
OBSTRUCTIVE PULMONARY DISEASE OR ASTHMA**

*Version 1.0
November 17, 1997*

**Prepared by
The COPD/Asthma Working Group***

**With support from
The Office of Performance Management
VHA Headquarters
Washington DC**

and

**The External Peer Review Program (EPRP)
Contractor and Subcontractor:
West Virginia Medical Institute, Inc.
Birch & Davis Associates, Inc.
Contract No. V101 (93) P-1369**

***See Directory in Appendices for Listing of Participants**

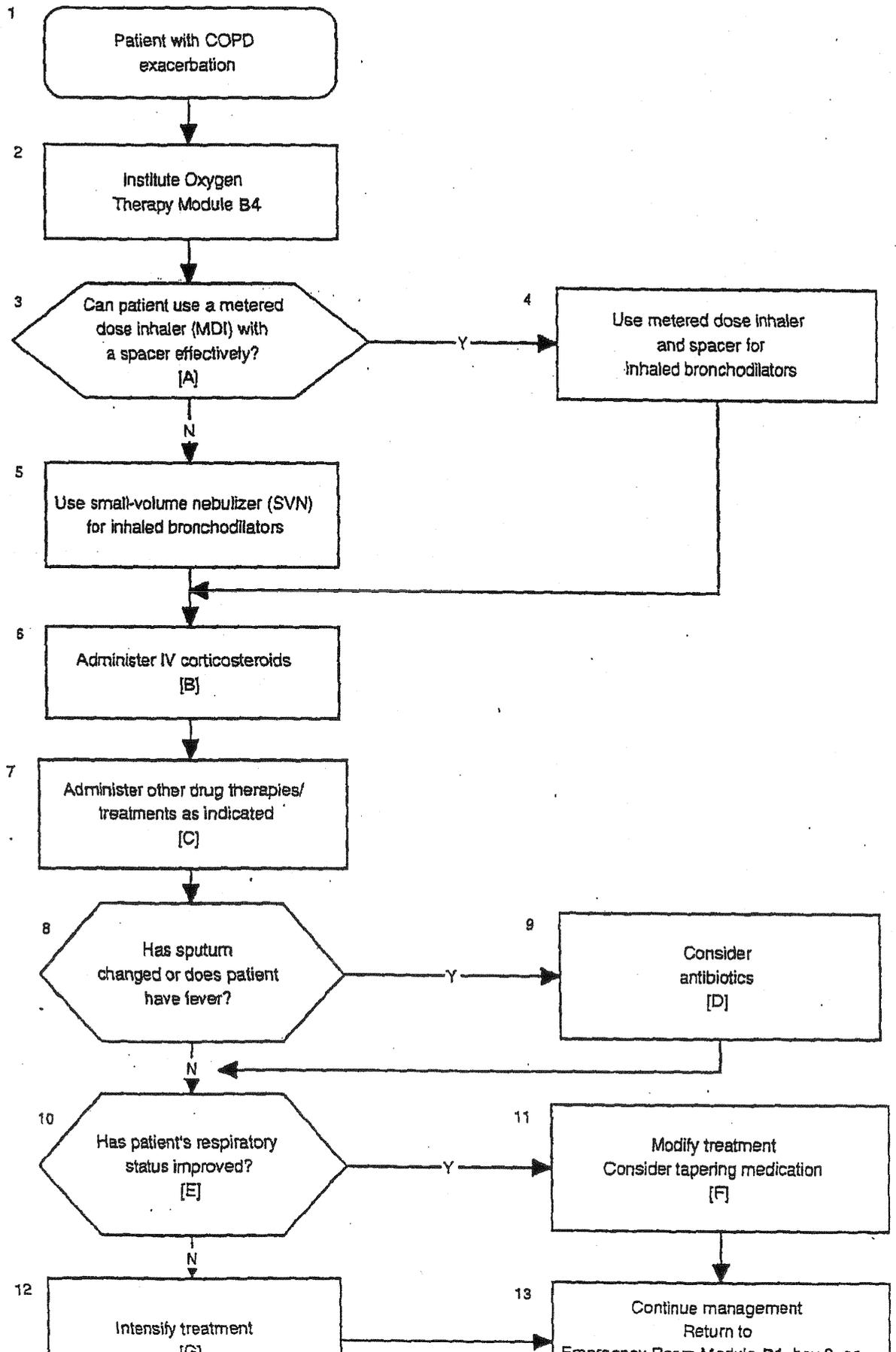
- If originally asymptomatic with an FEV₁ <50 percent and on therapy, then reevaluate for improvement or begin trial of therapy with inhaled anticholinergic (IAC). A trial of IAC therapy is recommended in apparently asymptomatic patients with an FEV₁ of less than 50 percent of predicted, since this degree of obstruction is usually associated with dyspnea. This is based on the well-known phenomenon of patients "adapting to their disability." Such a lack of symptoms may result from the patient's avoiding activities or simply thinking along the lines of "Doesn't everyone get short of breath doing this activity at my age?"

Ipratropium (without prn inhaled beta2-agonist, since it is not needed for rescue medication) is generally the first choice in a trial of therapy, with improvement in function or activities of daily living being used to guide therapy (see Annotation G). If ipratropium is ineffective or produces a less-than-optimal effect, add a short-acting inhaled beta2-agonist on a regular schedule (i.e., not prn) as combination therapy. A long-acting inhaled beta2-agonist may be substituted for the short-acting inhaled beta2-agonist if usage warrants. For further details on use of ipratropium and beta2-agonists, see Annotations E, F, and G. If there is no improvement or if symptoms worsen, the trial should be discontinued.

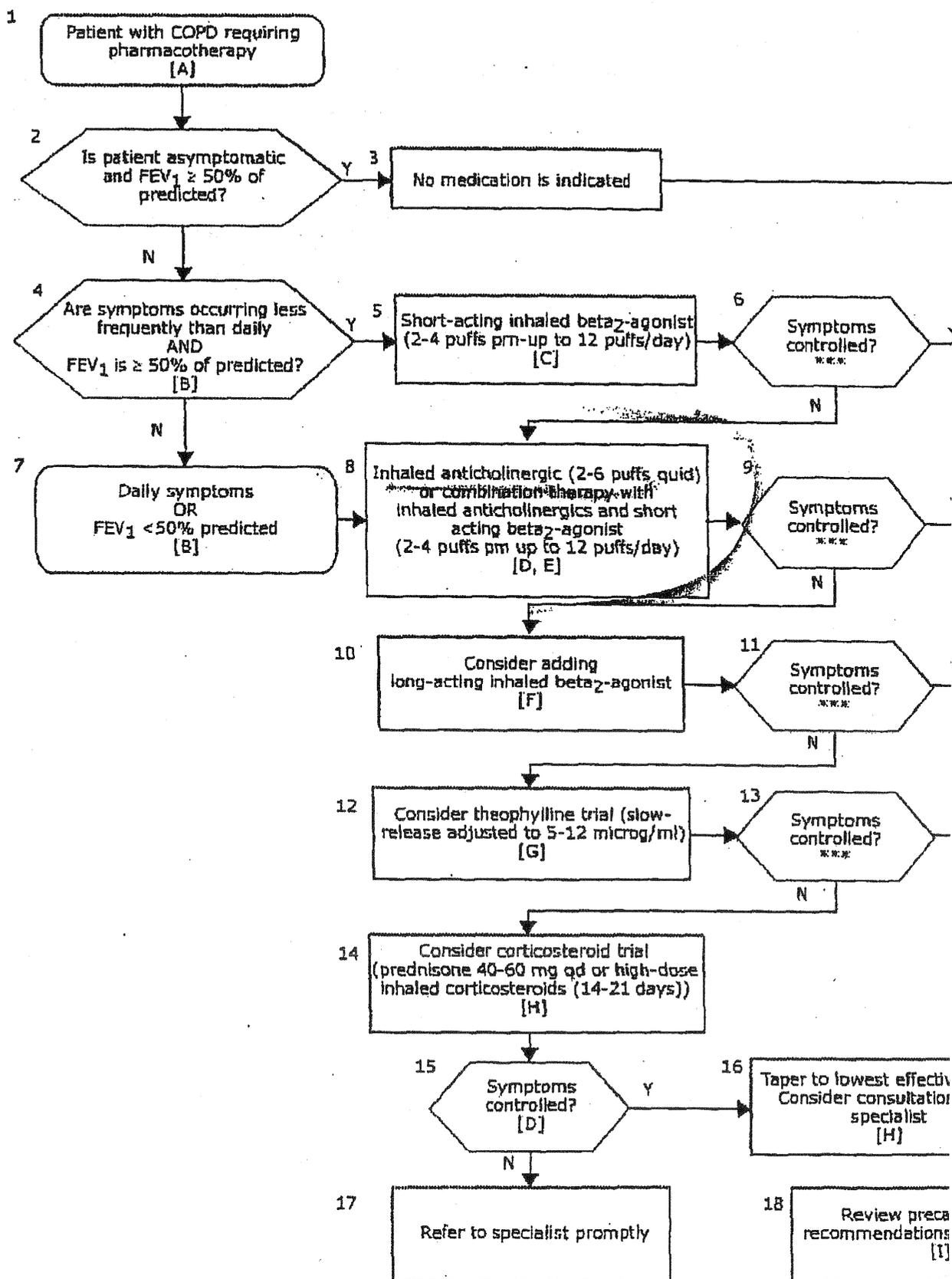
Ipratropium and short-acting inhaled beta2-agonists in typical doses (2 to 4 inhalations) on a scheduled rather than prn use are generally equally effective as bronchodilators, although some studies suggest that ipratropium has a greater peak and a longer duration of action. The side effects of each are similar, except for increases in heart rate and tremor (neither of which is typical at these doses) occur almost exclusively with beta2-agonists. Dyspnea may be improved to a greater extent with inhaled beta2-agonist. Some patients will have a response to one but not the other, so in any trial of therapy, both should be tried if improvement is not optimal with the first choice. There is evidence that ipratropium improves baseline pulmonary function (after withholding ipratropium for 6 to 12 hours) whereas beta2-agonists do not.

MANAGEMENT OF PERSONS WITH COPD OR ASTHMA
Inpatient Management of COPD
Pharmacotherapy

B3



Algorithm A2: Pharmacotherapy



***** Assure adherence to medication treatment, before escalating therapy**

in daily living can be used to guide therapy. The risk of toxicity at higher doses appears to be relatively low compared to inhaled beta₂-agonists.

5. The sequence of administration of ipratropium and SAIBA does not generally make any difference in the bronchodilator benefit.

EVIDENCE

Baseline FEV₁ and FVC increased within 90 days after ipratropium initiation: Rennard 1996. LE=B, SR=IIa

Ipratropium 40 µg qid (2 puffs) or metaproterenol 1.5mg qid by inhalation were equally efficacious and safe over a 90-day period: Tashkin 1986. LE=A, SR=I

No difference between 200 µg albuterol (2 puffs) and 40 µg ipratropium in magnitude, but duration was 1 hour longer with ipratropium on day 85: Combivent 1994. LE=A, SR=I

Ipratropium produced more and longer bronchodilation than did albuterol: Braun 1989. LE=B, SR=IIa

The distance walked was greater with 7 days of albuterol (180 µg, 2 puffs) or ipratropium (36 µg) qid (2 puffs); also dyspnea was less with albuterol: Blosser 1995. LE=B, SR=IIa

Of 80 responsive patients in a group of 100, 16 responded only to albuterol; 17 responded only to ipratropium; and 47 responded to both: Nisar 1992. LE=C, SR=IIa

Between 6 and 14 puffs of ipratropium (240 µg) produced maximum increase in pulmonary function: Ikeda 1995. LE=B, SR=I

160 µg of ipratropium (8-9 puffs) is needed to give maximum benefit in pulmonary function and to give any benefit at all with exercise: Ikeda 1996. LE=B, SR=I

0.4 mg of nebulized ipratropium provided a maximum response in pulmonary function. Suggested this was equivalent to 160 µg (8-9 puffs) from MDI: Gross 1989. LE=B, SR=IIa

E. Combination Therapy with Inhaled Anticholinergics and Short Acting Beta₂-Agonists

OBJECTIVE

To initiate or adjust appropriate therapy with a combination of inhaled SAIBA:

ANNOTATION

1. Patients with COPD whose symptoms are inadequately controlled with the recommended doses of either an inhaled short acting inhaled beta₂-agonist or ipratropium should be treated with a combination of both inhaled agents. The combination at recommended doses provides added symptomatic benefit without incurring the risk of toxicity from using very high doses of single agents.
2. SAIBA may be added to ipratropium as regularly scheduled medications, typically two to four puffs qid, as well as additional pm dosing, to a usual recommended maximum of 12 puffs per day. Demonstration of an acute improvement in FEV₁ is not necessary in order to obtain clinical benefit. The lack of an immediate bronchodilator response should not preclude a clinical trial of these medications.
3. As the dose of ipratropium or inhaled SAIBA increases, the added benefit becomes less from the other agent, but some patients will have an added benefit even with high doses of each. There is no way to predict, other than in a trial of therapy, which patients will have this combined effect.
4. A product that dispenses 90 µg albuterol and 18 µg ipratropium per puff from one metered dose inhaler is available commercially (Combivent™). This should not generally be used as a first line agent, but may provide enhanced compliance and resultant benefit in patients who require combination therapy. Patient taking a regularly scheduled combination inhaler should continue to use a SAIBA for breakthrough symptoms.



THE SECRETARY OF VETERANS AFFAIRS
WASHINGTON

CENTRAL OFFICE
WASHINGTON, DC
U.S. OFFICE OF
SPECIAL COUNSEL

November 18, 2005

2005 NOV 19 AM 9:55

Mr. Scott J. Bloch
U.S. Office of Special Counsel
1730 M Street, NW
Suite 300
Washington, DC 20036-4505

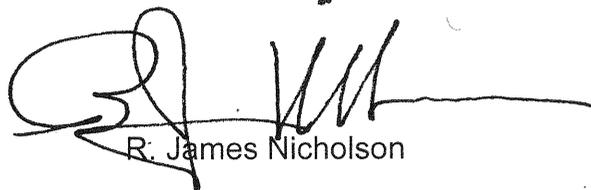
Dear Mr. Bloch:

Your letter dated September 15, 2005, outlines allegations of poor respiratory care at the VA Medical Center, Miami, FL, by a previously employed respiratory therapist, Mr. Gary Dilorenzo (Office of Special Counsel File Number DI-05-1801). I asked the Under Secretary for Health to review this matter and take any actions deemed necessary under 5 U.S.C. § 1213(d)(5). He, in turn, directed the Office of the Medical Inspector (OMI) to investigate the disclosures and report on its findings. The OMI's conclusions are set forth in the enclosed report. In short, the OMI found the complainant's allegations to be unsubstantiated.

For your information, this complaint was previously investigated by the Office of the Inspector General (OIG) in response to the complainant's contacting the IG Hotline on May 4, 2005, with similar concerns (Hotline Case Number 2005 02199-HL-0588). The Hotline Division forwarded the case to the OIG's Office of Health Inspection (OHI), which investigated the case. Based upon its review and an Administrative Board of Investigation conducted by the medical center, the OHI did not substantiate the complainant's allegations and closed the case.

Both the OHI and the OMI identified areas of improvement which are outlined in the report. These areas of improvement have been discussed with medical center senior management and they will develop an action plan to address the findings.

Sincerely yours,



R. James Nicholson

Enclosures

Office of the Medical Inspector Report on its Findings

Date

U.S. OFFICE OF SPECIAL COUNSEL
1730 M. Street, N. W. Suite 300
Washington, DC 20036-4505

Re: OSC File N. DI-05-1801

Introduction

The Office of the Medical Inspector (OMI) was asked by the Principal Deputy Under Secretary for Health to review the clinical issues related to a complaint lodged with the Office of Special Counsel (OSC) by a respiratory therapist employed at the VA Medical Center, Miami, FL (the Medical Center) regarding events that took place between March 6, 2005, and May 13, 2005. The complainant alleges that patients with pulmonary disease were not receiving proper treatment at the Medical Center. More specifically, the complainant alleges:

#1. In order to cut costs, the Medical Center management instructed medical personnel to incorrectly administer dosages of two medications, albuterol sulfate and ipratropium bromide, via nebulizer to patients receiving respiratory treatments. The complainant advised the OSC that albuterol sulfate comes in packages containing 2.5 milligrams (mg) of albuterol in 3.0 cubic centimeters (cc) of saline solution and ipratropium bromide comes in packages containing 0.5 mg of ipratropium bromide in 3.0 cc of saline solution; and that management has instructed the medical staff to mix the albuterol sulfate and ipratropium bromide packages together in order to administer them at the same time. The complainant alleges that this procedure has the effect of reducing the efficacy of each drug by approximately one-half, as it doubles the amount of saline solution.

#2. Management instructs medical personnel to administer these drugs at incorrect time intervals.

#3. Management directs medical personnel to falsely claim on a patient's medical record that the medication was administered at correct intervals.

Facility Profile

The Miami VA Medical Center and its attached four-story nursing home are located on a 26.3 acre campus. The Medical Center opened in 1968 and provides general medical, surgical, and psychiatric services; it also serves as an AIDS-/HIV Center, a Prosthetic Treatment Center, Spinal Cord Injury Rehabilitative Center, and Geriatric Research Education and Clinical Center. The facility is recognized as a Center of Excellence in Spinal Cord Injury Research and Substance Abuse Treatment.

Date

U.S. OFFICE OF SPECIAL COUNSEL
1730 M. Street, N. W. Suite 300
Washington, DC 20036-4505

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The Medical Center operates a 285-bed tertiary care teaching hospital and a 144-bed nursing home care unit. A full range of inpatient, including open heart surgery, and outpatient care is provided, including beds in medicine (82), surgery (30), intermediate care (36), neurology (5), psychiatric rehabilitation (58), psychiatry (32), rehabilitation medicine (6), and spinal cord (36). The Medical Center is also responsible for two major Satellite Outpatient Clinics, two Readjustment Counseling Centers, and several Community Based Outpatient Clinics.

The Medical Center has several affiliations but its primary affiliation is with the University of Miami School of Medicine. It has research programs in diseases affecting bones and joints, prostate disorders, mental health, HIV, dental health and is conducting special studies in infectious diseases, neurological disorders, and renal diseases. Residency training programs are provided to 150 residents in most of the medical and surgical subspecialties, as well as in pathology, psychiatry, and radiology. Other training programs exist in nursing, audiology/speech pathology, pharmacy, social work, nutrition and food service, nuclear medicine, radiology, and physical and occupational therapy.

Methods for Conducting the Investigation

The OMI contacted the Medical Center to notify the Director of the complaint and of the OMI's plan to conduct a site visit. The site visit took place October 3, 2005 –October 5, 2005, with the Medical Center staff providing full cooperation. The OMI team consisted of the OMI's Chief of the Clinical Investigation Division (a registered nurse) from VA Central Office, a Chief of Pulmonary Critical Care and Occupational Medicine (a physician) and a Chief Respiratory Therapist; the latter two are from another VA medical center. The team toured units where a large number of respiratory nebulizer treatments are performed: the medical intensive care unit (MICU), and two medical wards. The team spoke briefly with three patients about their satisfaction with their respiratory treatments; observed the administration of two nebulizer treatments and one metered dose inhaler; assessed the equipment used in the administration of treatments; and observed the documentation of treatments provided. As discussed in greater detail below, the team also reviewed the drug manufacturers' package insert information, national VHA clinical guidelines, local policy related to the administration of the medications in respiratory therapy treatments, and 42 individual electronic medical records of patients treated during the time frame noted in the complaint. The team additionally conducted interviews with 32 Medical Center staff.

The OMI team interviewed the following leadership and clinical staff: Director; Chief of Staff; Associate Director; Chief Nurse; Chief, Quality Management; Risk Manager; Patient Advocate; Chief, Human Resources; Compliance Officer; Chief, Respiratory Therapy; Chief Medical Resident; Chief, Pulmonary Care; Administrative Officer of the Medicine Service; and a respiratory therapy (RT) evaluator. There were four group interviews: one with three night shift RTs; another with two day shift RTs and two evening shift RTs; another with pharmacy personnel including the Chief, Pharmacy Service, three pharmacy staff and two pharmacy technicians; and a final group of five staff nurses.

It should be noted that on May 4, 2005, the complainant contacted the Inspector General's (IG) Hotline and expressed similar concerns about the delivery of respiratory care at the Medical Center. The Hotline Division forwarded the case (Hotline Case Number 2005 02199-HL-0588) to the Office of Healthcare Inspections (OHI) who investigated the case. Following an Administrative Investigative (AI) conducted by the Medical Center in June 2005, OHI found no improprieties related to the administration of the two medications; however, areas needing improvement were identified:

a) improve consistent documentation of respiratory treatments, b) improve staffing of the respiratory unit, c) improve recruitment and retention strategies for respiratory therapists, and d) clarify policy on the administration of medications via aerosol delivery devices.

Summary of the Evidence

a.) Respiratory Care Unit (RCU)

The Respiratory Care Unit (RCU) is under the direction of the Chief, Medical Service with 22 full time equivalent employees (FTEEs) and two vacancies. There is a Chief RT, an Assistant Chief (who runs the blood gas laboratory), and two RT evaluators (one on day shift and one on night shift).

The Medical Center has had problems recruiting and retaining RTs; most of the staff interviewed attributed this to non-competitive salaries. The RCU had 3.6 FTEEs that remained vacant for an extended period of time. In a facility-wide initiative to reduce cost, the Medical Service reduced RCU's FTEEs by permanently eliminating the 3.6 FTEEs, which, in the opinion of many of the staff interviewed, leaves the RCU short of staff.

The RTs are responsible for the administration of the medications albuterol sulfate and ipratropium bromide. Albuterol sulfate is a beta2-adrenergic short-acting bronchodilator which has been shown to have positive effects in the form of bronchial smooth muscle relaxation. It is indicated for the relief of bronchospasm in patients two years of age and over with reversible obstructive airway disease and acute attacks of bronchospasm. Albuterol sulfate comes in a 2.5 mg dose in 3.0 cc of saline solution. Ipratropium bromide is a long-acting, inhaled anticholinergic bronchodilator that is administered either alone or with other bronchodilators, especially beta adrenergics. It is indicated for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Ipratropium bromide comes in a package containing 0.5 mg in 3.0 cc of saline solution

b.) Manufacture Recommended Use

As mentioned in the introductory paragraph of this communication, the complainant stated that the "management" had incorrectly requested that medical personnel mix the albuterol and the ipratropium bromide prior to administering it by inhalation to patients. He stated that such mixing was endangering the health of the veterans so-treated, because

it was diluting the medications, causing them extreme discomfort and at heightened risk for cardiac arrest. It is important to note the inaccuracy of these allegations. These two medications, both used for treatment of bronchospasm in individuals with obstructive lung disease and/or asthma, are very frequently used as a mixed combination. In fact, the FDA-approved labeling for ipratropium bromide states “ipratropium bromide inhalation solution has been shown to be a safe and effective bronchodilator when used in conjunction with beta adrenergic bronchodilators.” (see attachments A & B).

Additionally, it is relevant to note that there is a fixed combination aerosol, with the trade name Combivent®, which contains both ipratropium bromide and albuterol. In regard to the question of dilution, it should be noted that any aerosol solution used for inhalation treatments is to be inhaled until the vial is empty. The pharmacologic effects are dependent upon the amount of the medication, not its dilution. When an inhaled medication is used, there is always a tiny residual amount (called the “dead volume”) which may be left in the inhalation system. This residual, in terms of amount of drug, will actually be less if the medications are in a larger volume (see Hess, D, Fisher, D., Williams, P, Pooler, S. and Kacmarek, RM, *Medication nebulizer performance. Effects of diluent volume, nebulizer flow, and nebulizer brand.* 1996, Chest:Aug;110(2):498-505). So there may be more complete delivery in a larger volume of the same mg. dose than in a smaller volume.

c.) Clinical Practice Guideline

VHA’s Clinical Practice Guideline for the Management of Persons with Chronic Obstructive Pulmonary Disease or Asthma (Version 1.0, November 17, 1997) clearly supports the mixing of these two medications as a more efficacious way of managing bronchospasm. Attachment C, practice guideline flowchart.

d.) RCU Policy

The AI conducted in June 2005 found that the Medical Center policy, *Selection of Aerosol Delivery Device Code, 7.0* discussed the administration of medications by drug class and did not address the specific medications administered by the RTs. As noted above, the OHI also identified that the policy needed to be clarified. At the time of the OMI visit, a new policy had been drafted and was in the concurrence process; it identifies how albuterol sulfate and ipratropium bromide are to be mixed when ordered. It states, “Orders call for the combination of Ipratropium Bromide with Albuterol Sulfate or Metaproterenol Unit Dose for delivery by small volume nebulizer (SVN) will be accomplished by adding one unit dose vial of each medication to the SVN’s medicine cup. The treatment must be administered within one hour of missing the medication to insure stability of combined medications.”

e.) Staff Interviews

Medical Center leadership (Director, Chief of Staff Associate Director, and Nurse Executive) all support the use of overtime to cover staffing shortages in the RCU to meet patient care needs. In addition, leadership said that the cost of each of the two

medications in question is minimal and would not be targeted in an effort to cut costs. When asked directly, each denied instructing medical personnel to administer albuterol sulfate and ipratropium bromide at incorrect intervals and to document falsely that they were given as ordered.

The Compliance Officer provides education to the entire facility staff about reporting unethical or fraudulent behavior at periodic training and in new employee orientation. The Compliance Officer developed a matrix reporting structure for employees, patients, and family members. Exit interviews with staff leaving the Medical Center are also conducted. At the complainant's exit interview, concerns were reported regarding the administration of respiratory treatments. In addition, the Compliance Officer instructed the complainant on how to report his concerns, which he did. The Compliance Officer has no independent knowledge of unethical behavior relating to the three allegations lodged by the complainant.

The Chief, Pulmonary Medicine and the Chief Medical Resident had no knowledge of any unethical behavior related to the allegation lodged by the complainant, nor did they instruct anyone to carry out the acts described by the complainant. They both agreed that the RCU is short of staff and that the RTs do a good job caring for patients.

Nurses from the medical wards, the MICU, and nursing home were interviewed. They also believe that the RCU is short of staff, and on occasion the nurses will start the treatments when the RTs are busy. They acknowledge that it would be difficult to give every treatment as prescribed with the current number of RTs and with all of the unit activities. The nurses provide the nebulizer treatment in the nursing home with support from the RCU when needed. A senior RT provides annual competency reviews for the nursing home staff as well as training and education during new employee orientation for clinical staff.

Pharmacy staff expressed that mixing albuterol sulfate and ipratropium bromide in a nebulizer is the appropriate way to administer these medications and that this practice is long standing and is preferred. They identified no contraindications to this mixing. They described the cost of the two drugs as "pennies" with no significant budgetary impact. They too asserted that the cost of these medications is minute and as such does not support the allegations of the complainant.

The Chief, RCU indicated that when an order is written for respiratory treatment, a request prints out in the RCU office; however, since there is no administrative support in the office, the order may sit until a RT returns to the unit. Once an order is received, an RT evaluator will evaluate the patient and review the order. If there are concerns about either, the evaluator will contact the prescribing physician for clarification. If no concerns are identified, the treatments will be initiated. The Chief believes the RT staff to be professional, well trained, and dedicated to providing quality care to veterans. Some barriers to completing all ordered therapies or documenting all therapies provided are the large workload carried by each RT, charting treatments in as many as four places, and having to wait for a computer to document treatments. The Chief, RCU denies asking her

staff to falsify medical records by charting treatments that were not given or advising staff to give treatments at less frequent intervals.

The RTs interviewed denied that anyone told or asked them to falsify medical records or give respiratory treatments at less frequent intervals to save money or for any other reason. The RTs said that they would not do this because it would be a risk to their licenses and professional careers. They do admit that they do the best they can, given the staffing shortage of RTs and high volume of treatments ordered. If they are unable to get to a treatment they pass it on to the next shift.

f. Observations

The OMI team observed the administration of two nebulizer treatments. The two medications, albuterol sulfate and ipratropium bromide, were obtained from the Pyxis or medication cart, poured into a small-volume nebulizer as 5-6 cc of liquid, and administered by face mask. The RTs appropriately identified the patient, explained the treatment, assessed the patient, took vital signs (before and after), and provided patient education. The treatment took approximately 13 minutes to administer. The RTs use a work log to document treatments provided, which are later transcribed into the electronic medical record on a template especially designed for RT treatments. There was no evidence of failure, non-availability, or shortages of any equipment.

g. Medical Record Review

During the period in question, March 6, 2005, to May 13, 2005, 154 patients were ordered albuterol sulfate and ipratropium bromide to be given as a mixture. A review of 42 of the 154 patient's electronic medical records revealed that when RT treatments are ordered to be given "now" they were generally not given in a timely fashion, few patients received all of the treatments ordered, and there was inconsistent documentation as to when or why treatments were missed. If allegation #3 were true (falsification of records), the review would have revealed more consistent documentation and fewer missed treatments. In sum, the medical record review does not support the claim that staff falsely documented that treatments were given at the correct interval when they were not.

It was clear to the OMI team that several factors contribute to patients not receiving all of their treatments: patients are often out of their rooms for tests or other reasons, a patient emergency that requires and diverts the full attention of the RT, and the staffing shortage in the RCU.

The Quality Manager, Risk Manager, and the Patient Advocate were each asked to review their records for the period of the complainant's employment to determine if there were any specific complaints about respiratory care; adverse events resulting in root cause analyses (RCAs) being conducted about respiratory care; or peer review or other quality measures that identified issues with the quality of respiratory care provided. None were reported.

In addition, none of those officials reported having any knowledge of leadership having unethically instructed staff to improperly administer the drugs at issue here, as alleged by complainant.

Conclusions

Allegation # 1: *OMI Conclusion: The medications come packaged as described by the complainant; however, mixing albuterol sulfate and ipratropium bromide in the treatment of bronchospasm is a long standing policy and is supported by the manufacturer's recommendations. VHA Clinical Practice Guideline for the Management of Person with Chronic Obstructive Pulmonary Disease or Asthma also supports this technique. The cost of these medications is minimal and there would be no cost savings advantage to mixing them.*

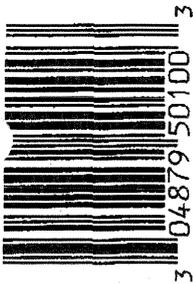
Allegation #2: *OMI Conclusion: The OMI found no evidence that management, at any level, instructed medical personnel to administer these medications at incorrect intervals.*

Allegation #3: *OMI Conclusion: The OMI found no evidence that management, at any level, instructed medical personnel to falsely claim on a patient's medical record that they gave the patient the medication at the correct intervals.*

In summary, the OMI found that the mixing albuterol sulfate and ipratropium bromide is standard practice and does not represent a threat to veterans' health. No violation of clinical practice or apparent violation of any law, rule, or regulation was found. However, the OMI agrees with the findings of the OIG-OHI investigation and recommends that the Medical Center:

- 1.) Improve documentation by the RTs
- 2.) Fully staff the RCU
- 3.) Improve recruitment and retention strategies for RTs.

An action plan will be forthcoming from the Medical Center.



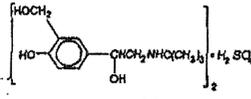
ATTACHMENT A

Albuterol Sulfate Inhalation Solution, 0.083%*

*Potency expressed as albuterol.

DESCRIPTION

Albuterol Sulfate Inhalation Solution is a relatively selective beta₂-adrenergic bronchodilator (see CLINICAL PHARMACOLOGY). Albuterol sulfate, USP, the racemic form of albuterol, has the chemical name *1*-[1-(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene- α,α -diol sulfate (2:1) (salt) and the following structural formula:



Albuterol sulfate has a molecular weight of 576.71, and the molecular formula is $(C_{21}H_{27}NO_7)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

Albuterol Sulfate Inhalation Solution requires no dilution before administration by nebulization.

Each milliliter of Albuterol Sulfate Inhalation Solution contains 0.83 mg of albuterol (as 1 mg of albuterol sulfate) in an isotonic, sterile, aqueous solution containing sodium chloride; sulfuric acid is used to adjust the pH to between 3 and 5. Albuterol Sulfate Inhalation Solution contains no buffering agents or preservatives.

Albuterol Sulfate Inhalation Solution is a clear, colorless to light yellow solution.

CLINICAL PHARMACOLOGY

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta₂-adrenergic receptors compared with isoproterenol. While it is recognized that beta₂-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that 10% to 50% of the beta-receptors in the human heart may be beta₂-receptors. The precise function of these receptors has not been established.

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects.

Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-O-methyl transferase.

Pharmacokinetics: Studies in asthmatic patients have shown that less than 20% of a single albuterol dose was absorbed following either IPPB (intermittent positive-pressure breathing) or nebulizer administration; the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. Following a 3-mg dose of nebulized albuterol in adults, the maximum albuterol plasma levels at 0.5 hours were 2.1 ng/mL (range, 1.4 to 3.2 ng/mL). There was a significant dose-related response in FEV₁ (forced expiratory volume in one second) and peak flow rate. It has been demonstrated that following oral administration of 4 mg of albuterol, the elimination half-life was 5 to 6 hours.

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the brain barrier (pituitary and pineal glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (mini-pigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methyldanthines were administered concurrently. The clinical significance of these findings is unknown.

Clinical Trials: In controlled clinical trials in adults, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by FEV₁. FEV₁ measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in FEV₁ over baseline values) continued for 3 to 4 hours in most patients, with some patients continuing up to 6 hours.

within 2 to 20 minutes following single doses of albuterol inhalation solution. An increase of 15% or more in baseline FEV₁ has been observed in children aged 5 to 11 years up to 6 hours after treatment with doses of 0.10 mg/kg or higher of albuterol inhalation solution. Single doses of 3, 4, or 10 mg resulted in improvement in baseline PEFR that was comparable in extent and duration to a 2-mg dose, but doses above 3 mg were associated with heart rate increases of more than 10%.

INDICATIONS AND USAGE

Albuterol Sulfate Inhalation Solution is indicated for the relief of bronchospasm in patients 2 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.

CONTRAINDICATIONS

Albuterol Sulfate Inhalation Solution is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

WARNINGS

Paradoxical Bronchospasm: Albuterol Sulfate Inhalation Solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Albuterol Sulfate Inhalation Solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

Cardiovascular Effects: Albuterol Sulfate Inhalation Solution, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Albuterol Sulfate Inhalation Solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Albuterol Sulfate Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Albuterol Sulfate Inhalation Solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

Use of Anti-inflammatory Agents: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids.

PRECAUTIONS

General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Repeated dosing with 0.15 mg/kg of albuterol inhalation solution in children aged 5 to 17 years who were initially normokalemic has been associated with an asymptomatic decline of 20% to 25% in serum potassium levels.

Information For Patients: The action of Albuterol Sulfate Inhalation Solution may last up to 6 hours or longer. Albuterol Sulfate Inhalation Solution should not be used more frequently than recommended. Do not increase the dose or frequency of Albuterol Sulfate Inhalation Solution without consulting your physician. If you find that treatment with Albuterol Sulfate Inhalation Solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using Albuterol Sulfate Inhalation Solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, and tremor or nervousness. If you are pregnant or nursing, contact your physician about use of Albuterol Sulfate Inhalation Solution. Effective and safe use of Albuterol Sulfate Inhalation Solution includes an understanding of the way that it should be administered.

Drug compatibility (physical and chemical), efficacy, and safety of Albuterol Sulfate Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

See Illustrated Patient's Instructions for Use.

Drug Interactions: Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta-Blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Albuterol Sulfate Inhalation Solution, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Patient's Instructions for Use

Albuterol Sulfate Inhalation Solution, 0.083% *Potency expressed as albuterol.

Read complete instructions carefully before using.

1. Twist open the top of one Albuterol Sulfate Inhalation Solution unit-of-use container and squeeze the entire contents into the nebulizer reservoir (Figure 1).



Figure 1

2. Connect the nebulizer reservoir to the mouthpiece or face mask (Figure 2).

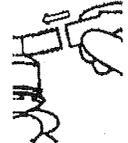


Figure 2

3. Connect the nebulizer to the compressor.
4. Sit in a comfortable, upright position; place mouthpiece in your mouth (Figure 3) or put the face mask; and turn on the compressor.



Figure 3

5. Breathe as calmly, deeply and evenly as possible until no more mist is formed in the nebulizer chamber (about 5 to 15 minutes); this point, the treatment is finished.
6. Clean the nebulizer (see manufacturer's instructions).

(continued on other side)

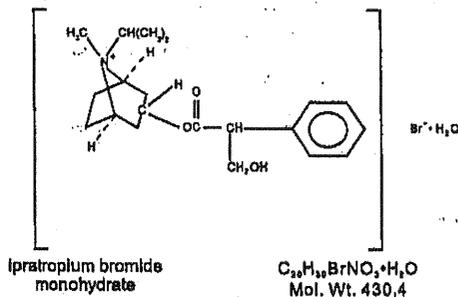


ATTACHMENT B

Rx only

Prescribing Information

DESCRIPTION The active ingredient in Ipratropium bromide inhalation solution is ipratropium bromide monohydrate. It is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (*endo, syn*)-(±); a synthetic quaternary ammonium compound, chemically related to atropine.



Ipratropium bromide is a white crystalline substance, freely soluble in water and lower alcohols. It is a quaternary ammonium compound and thus exists in an ionized state in aqueous solutions. It is relatively insoluble in non-polar media.

Ipratropium bromide inhalation solution is administered by oral inhalation with the aid of a nebulizer. It contains ipratropium bromide 0.02% (anhydrous basis) in a sterile, preservative-free, isotonic saline solution, pH-adjusted to 3.4 (3 to 4) with hydrochloric acid.

CLINICAL PHARMACOLOGY Ipratropium bromide is an anticholinergic (parasympatholytic) agent that, based on animal studies, appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increases in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) that are caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.

The bronchodilation following inhalation of Ipratropium bromide inhalation solution is primarily a local, site-specific effect, not a systemic one. Much of an administered dose is swallowed but not absorbed, as shown by fecal excretion studies. Following nebulization of a 2 mg dose, a mean of 7% of the dose was absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract. The half-life of elimination is about 1.6 hours after intravenous administration. Ipratropium bromide is minimally (0 to 9% *in vitro*) bound to plasma albumin and α_1 -acid glycoproteins. It is partially metabolized. Autoradiographic studies in rats have shown that ipratropium bromide inhalation solution does not penetrate the blood-brain barrier. Ipratropium bromide inhalation solution has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in those patient populations.

In controlled 12-week studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV₁ increases of 15% or more) occurred within 15 to 30 minutes, reached a peak in 1-2 hours, and persisted for periods of 4-5 hours in the majority of patients, with about 25-36% of the patients demonstrating increases of 15% or more for at least 7-8 hours. Continued effectiveness of Ipratropium bromide inhalation solution was demonstrated throughout the 12-week period. In addition, significant increases in forced vital capacity (FVC) have been demonstrated. However, Ipratropium

bromide inhalation solution did not consistently produce significant improvement in subjective symptom scores nor in quality of life scores over the 12-week duration of study. Additional controlled 12-week studies were conducted to evaluate the safety and effectiveness of Ipratropium bromide inhalation solution administered concomitantly with the beta adrenergic bronchodilator solutions: metaproterenol and albuterol compared with the administration of each of the beta agonists alone. Combined therapy produced significant additional improvement in FEV₁ and FVC. On combined therapy, the median duration of 15% improvement in FEV₁ was 5-7 hours, compared with 3-4 hours in patients receiving a beta agonist alone.

INDICATIONS AND USAGE Ipratropium bromide inhalation solution administered either alone or with other bronchodilators, especially beta adrenergics, is indicated as a bronchodilator for maintenance treatment of bronchoepasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

CONTRAINDICATIONS Ipratropium bromide inhalation solution is contraindicated in known or suspected cases of hypersensitivity to ipratropium bromide, or to atropine and its derivatives.

WARNINGS The use of ipratropium bromide inhalation solution as a single agent for the relief of bronchoepasm in acute COPD exacerbation has not been adequately studied. Drugs with faster onset of action may be preferable as initial therapy in this situation. Combination of ipratropium bromide inhalation solution and beta agonists has not been shown to be more effective than either drug alone in reversing the bronchoepasm associated with acute COPD exacerbation. Immediate hypersensitivity reactions may occur after administration of Ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchoepasm and oropharyngeal edema.

PRECAUTIONS General: Ipratropium bromide inhalation solution should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy or bladder neck obstruction.

Information For Patients: Patients should be advised that temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma or eye pain may result if the solution comes into direct contact with the eyes. Use of a nebulizer with a mouthpiece rather than a face mask may be preferable, to reduce the likelihood of the nebulizer solution reaching the eyes. Patients should be advised that Ipratropium bromide inhalation solution can be mixed in the nebulizer with albuterol or metaproterenol if used within one hour. Drug stability and safety of Ipratropium bromide inhalation solution when mixed with other drugs in a nebulizer have not been established. Patients should be reminded that Ipratropium bromide inhalation solution should be used consistently as prescribed throughout the course of therapy.

Drug Interactions: Ipratropium bromide inhalation solution has been shown to be a safe and effective bronchodilator when used in conjunction with beta adrenergic bronchodilators. Ipratropium bromide inhalation solution has also been used with other pulmonary medications, including methylxanthines and corticosteroids, without adverse drug interactions. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic potential at dietary doses up to 6 mg/kg/day of Ipratropium bromide. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg/day was unaffected by Ipratropium bromide inhalation solution administration. At doses above 90 mg/kg, increased resorption and decreased conception rates were observed.

Pregnancy TERATOGENIC EFFECTS

Pregnancy Category B. Oral reproduction studies performed in mice, rats and rabbits at doses of 10, 100 and 125 mg/kg respectively, and inhalation reproduction studies in rats and rabbits at doses of 1.5 and 1.8 mg/kg (or approximately 38 and 45 times the recommended human daily dose) respectively, have demonstrated no evidence of teratogenic effects as a result of Ipratropium bromide inhalation solution. However, no adequate or well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, Ipratropium bromide inhalation solution should be used during

Patient's Instructions for Use

Ipratropium Bromide Inhalation Solution, 0.02%

Read complete instructions carefully before using.

1. Twist open the top of one unit dose vial and squeeze the contents into the nebulizer reservoir (Figure 1).

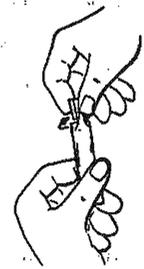


Figure 1

2. Connect the nebulizer reservoir to the mouthpiece or face mask (Figure 2).

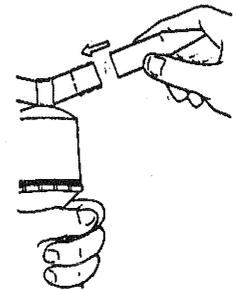


Figure 2

3. Connect the nebulizer to the compressor.

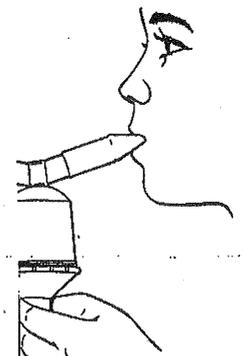


Figure 3

4. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 3) or put on a face mask and turn on the compressor. If a face mask is used, care should be taken to avoid leakage around the mask as temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma, or eye pain may occur if the solution comes into direct contact with the eyes.

**VETERANS HEALTH ADMINISTRATION
CLINICAL PRACTICE GUIDELINE FOR THE
MANAGEMENT OF PERSONS WITH CHRONIC
OBSTRUCTIVE PULMONARY DISEASE OR ASTHMA**

*Version 1.0
November 17, 1997*

**Prepared by
The COPD/Asthma Working Group***

**With support from
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and

**The External Peer Review Program (EPRP)
Contractor and Subcontractor:
West Virginia Medical Institute, Inc.
Birch & Davis Associates, Inc.
Contract No. V101 (93) P-1369**

***See Directory in Appendices for Listing of Participants**

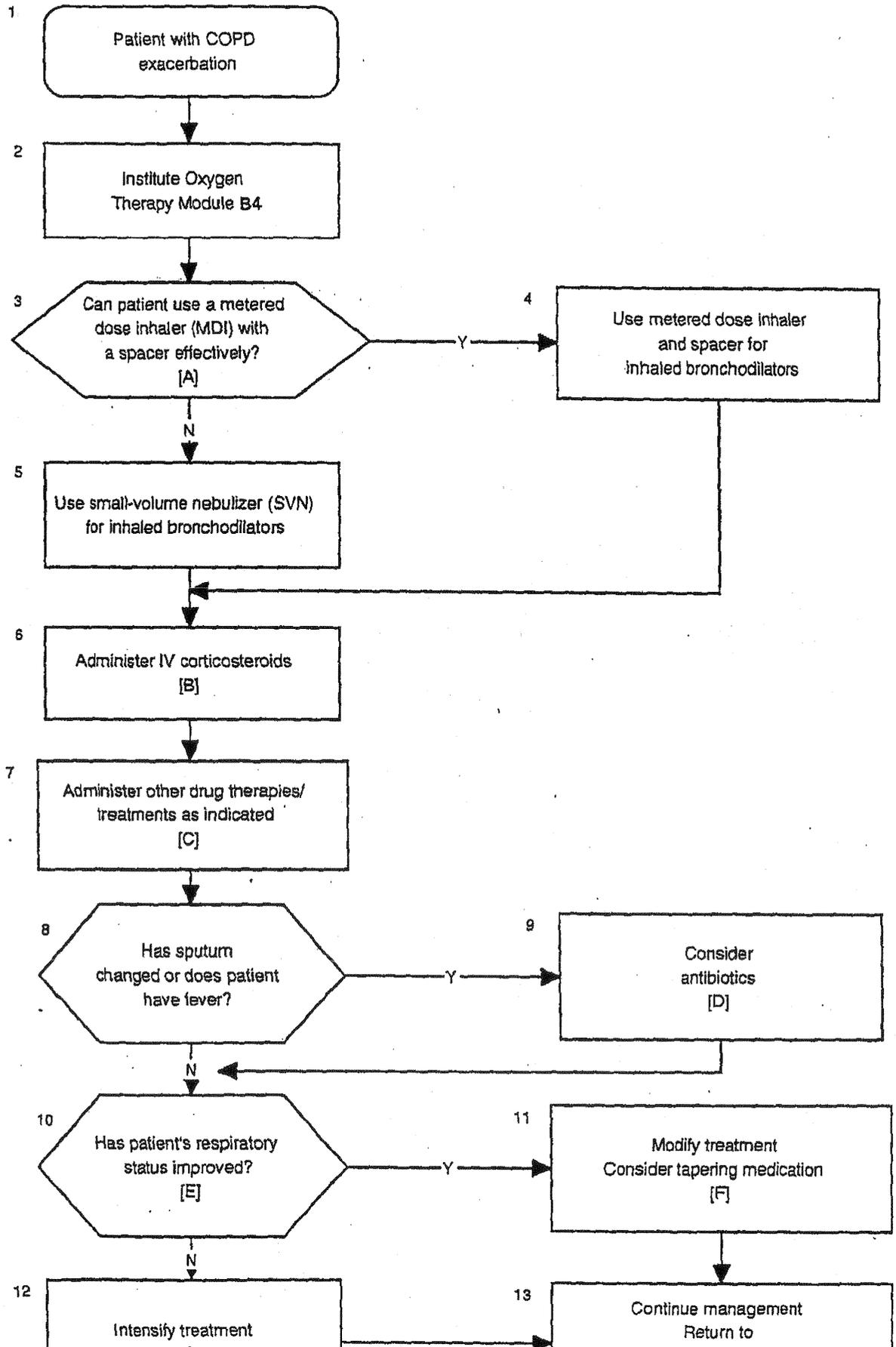
- If originally asymptomatic with an FEV₁ <50 percent and on therapy, then reevaluate for improvement or begin trial of therapy with inhaled anticholinergic (IAC). A trial of IAC therapy is recommended in apparently asymptomatic patients with an FEV₁ of less than 50 percent of predicted, since this degree of obstruction is usually associated with dyspnea. This is based on the well-known phenomenon of patients "adapting to their disability." Such a lack of symptoms may result from the patient's avoiding activities or simply thinking along the lines of "Doesn't everyone get short of breath doing this activity at my age?"

Ipratropium (without prn inhaled beta2-agonist, since it is not needed for rescue medication) is generally the first choice in a trial of therapy, with improvement in function or activities of daily living being used to guide therapy (see Annotation G). If ipratropium is ineffective or produces a less-than-optimal effect, add a short-acting inhaled beta2-agonist on a regular schedule (i.e., not prn) as combination therapy. A long-acting inhaled beta2-agonist may be substituted for the short-acting inhaled beta2-agonist if usage warrants. For further details on use of ipratropium and beta2-agonists, see Annotations E, F, and G. If there is no improvement or if symptoms worsen, the trial should be discontinued.

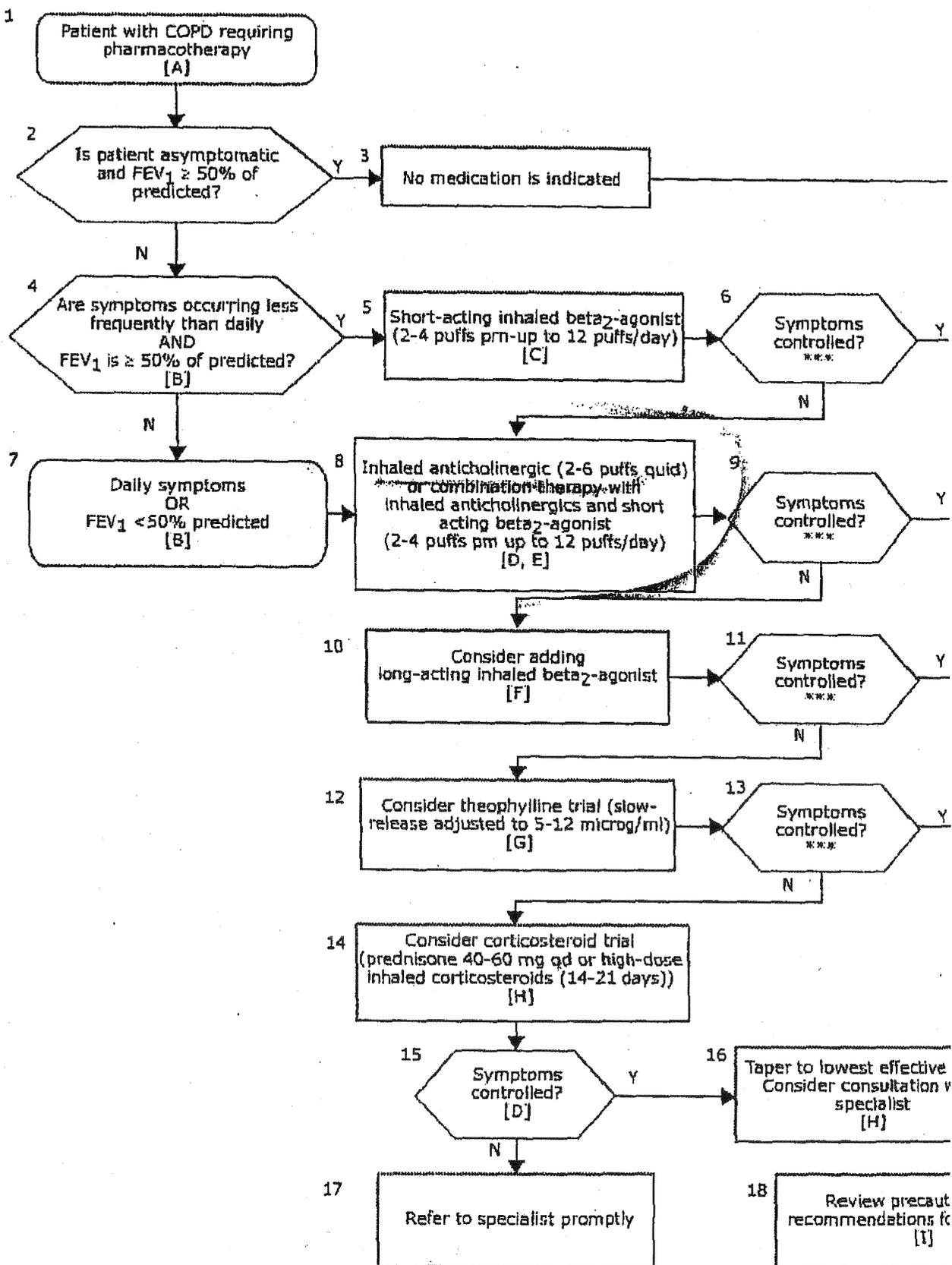
Ipratropium and short-acting inhaled beta2-agonists in typical doses (2 to 4 inhalations) on a scheduled rather than prn use are generally equally effective as bronchodilators, although some studies suggest that ipratropium has a greater peak and a longer duration of action. The side effects of each are similar, except for increases in heart rate and tremor (neither of which is typical at these doses) occur almost exclusively with beta2-agonists. Dyspnea may be improved to a greater extent with inhaled beta2-agonist. Some patients will have a response to one but not the other, so in any trial of therapy, both should be tried if improvement is not optimal with the first choice. There is evidence that ipratropium improves baseline pulmonary function (after withholding ipratropium for 6 to 12 hours) whereas beta2-agonists do not.

MANAGEMENT OF PERSONS WITH COPD OR ASTHMA
Inpatient Management of COPD
Pharmacotherapy

B3



Algorithm A2: Pharmacotherapy



***** Assure adherence to medication treatment, before escalating therapy**

in daily living can be used to guide therapy. The risk of toxicity at higher doses appears to be relatively low compared to inhaled beta₂-agonists.

5. The sequence of administration of ipratropium and SAIBA does not generally make any difference in the bronchodilator benefit.

EVIDENCE

Baseline FEV₁ and FVC increased within 90 days after ipratropium initiation: Rennard 1996. LE=B, SR=IIa

Ipratropium 40 µg qid (2 puffs) or metaproterenol 1.5mg qid by inhalation were equally efficacious and safe over a 90-day period: Tashkin 1986. LE=A, SR=I

No difference between 200 µg albuterol (2 puffs) and 40 µg ipratropium in magnitude, but duration was 1 hour longer with ipratropium on day 85: Combivent 1994. LE=A, SR=I

Ipratropium produced more and longer bronchodilation than did albuterol: Braun 1989. LE=B, SR=IIa

The distance walked was greater with 7 days of albuterol (180 µg, 2 puffs) or ipratropium (36 µg) qid (2 puffs); also dyspnea was less with albuterol: Blosser 1995. LE=B, SR=IIa

Of 80 responsive patients in a group of 100, 16 responded only to albuterol; 17 responded only to ipratropium; and 47 responded to both: Nisar 1992. LE=C, SR=IIa

Between 6 and 14 puffs of ipratropium (240 µg) produced maximum increase in pulmonary function: Ikeda 1995. LE=B, SR=I

160 µg of ipratropium (8-9 puffs) is needed to give maximum benefit in pulmonary function and to give any benefit at all with exercise: Ikeda 1996. LE=B, SR=I

0.4 mg of nebulized ipratropium provided a maximum response in pulmonary function. Suggested this was equivalent to 160 µg (8-9 puffs) from MDI: Gross 1989. LE=B, SR=IIa

E. Combination Therapy with Inhaled Anticholinergics and Short Acting Beta₂-Agonists

OBJECTIVE

To initiate or adjust appropriate therapy with a combination of inhaled SAIBA.

ANNOTATION

1. Patients with COPD whose symptoms are inadequately controlled with the recommended doses of either an inhaled short acting inhaled beta₂-agonist or ipratropium should be treated with a combination of both inhaled agents. The combination at recommended doses provides added symptomatic benefit without incurring the risk of toxicity from using very high doses of single agents.
2. SAIBA may be added to ipratropium as regularly scheduled medications, typically two to four puffs qid, as well as additional prn dosing, to a usual recommended maximum of 12 puffs per day. Demonstration of an acute improvement in FEV₁ is not necessary in order to obtain clinical benefit. The lack of an immediate bronchodilator response should not preclude a clinical trial of these medications.
3. As the dose of ipratropium or inhaled SAIBA increases, the added benefit becomes less from the other agent, but some patients will have an added benefit even with high doses of each. There is no way to predict, other than in a trial of therapy, which patients will have this combined effect.
4. A product that dispenses 90 µg albuterol and 18 µg ipratropium per puff from one metered dose inhaler is available commercially (Combivent™). This should not generally be used as a first line agent, but may provide enhanced compliance and resultant benefit in patients who require combination therapy. Patients taking a regularly scheduled combination inhaler should continue to use a SAIBA for breakthrough symptoms.