Preservatives in Nebulizer Solutions: Risks without Benefit

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Edetate disodium (EDTA) and benzalkonium chloride (BAC) are often present as preservative or stabilizing agents in nebulizer solutions used to treat asthma and chronic obstructive pulmonary disease. Benzalkonium chloride is a potent bronchoconstrictor when inhaled in concentrations similar to those in which it is present in these solutions. Inclusion of BAC (together with EDTA) in the ipratropium bromide (Atrovent) nebulizer solution resulted in paradoxic bronchoconstriction in some asthmatic patients and an overall reduction in bronchodilator efficacy. The presence of BAC in albuterol nebulizer solutions does not affect the short-term bronchodilator response to a single dose, although case reports suggest that its repeated use in patients with severe asthma may result in paradoxic bronchoconstriction. When inhaled by asthmatic subjects, EDTA also causes dose-dependent bronchoconstriction, although it is less potent than BAC. The use of preservative-free bronchodilator nebulizer solutions does not result in clinically significant bacterial contamination if they are dispensed in sterile unit-dose vials, in volumes and concentrations that do not require modification by the user. Despite this evidence, in the United States a number of solutions, including some preparations of albuterol, contain either BAC or EDTA. Current regulations do not require that the concentration of preservatives be documented on the product; however, considerably different doses of BAC are delivered with different products. For example, a standard 2.5-mg dose of albuterol nebulizer solution contains 50 µg of BAC when administered from the multidose dropper bottle and 300 µg from the unit-dose screw-cap product. Furthermore, it is legal for pharmacists to substitute or compound solutions containing high concentrations of BAC when the physician has prescribed a preservative-free product. We recommend that the United States follow the practice of most Western countries and withdraw bronchodilator nebulizer solutions that contain preservatives such as BAC. We further recommend that the solutions should be prepared under sterile conditions, formulated preservative free, and made available in unit-dose vials.
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OUTLINE

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Nebulization is a common method of administering pharmacologic agents in the treatment of a

number of different respiratory disorders including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, lung (hyaline membrane) disease of immaturity, and immunodeficiency disorders. In particular, it has gained widespread use in the treatment of asthma and COPD, as it allows high doses of bronchodilators to be delivered to the lungs despite the presence of airflow obstruction. Although the efficacy of bronchodilator nebulizer therapy was established soon after its introduction, it was not long before reports began to appear of paradoxic bronchoconstriction associated with it.[1, 2] Factors associated with this response include osmolality,[3, 4] acidity,[5, 6] and chemical additives such as preservatives[7, 8] and stabilizers[7] in the solution. In addition, formation of a weak β-blocking metabolite from isoproterenol was reported.[9]

The potential for chemical additives to cause paradoxic bronchoconstriction was first recognized with an isoproterenol nebulizer solution that contained sodium metabisulfite.[1, 2] When administered to asthmatic patients the solution had the potential to worsen the degree of airflow obstruction as a consequence of sulfur dioxide (SO_2) released from metabisulfite. Sulfur dioxide levels ranging from between 0.1 and 6.0 parts per million (ppm) were measured in nebulizer solutions commercially available for bronchodilator use.[8–11] The clinical significance of these levels is suggested by the fact that sensitive asthmatics may experience bronchospasm while exercising when inhaling as little as 0.1 ppm SO_2,[12] and even nonasthmatics may develop bronchospasm at a level of 6 ppm.[13] These findings led to the removal of sulfites from most (although not all) commercially available nebulizer solutions.

Benzalkonium Chloride

The preservative most commonly present in nebulizer solutions was benzalkonium chloride (BAC), a mixture of quaternary benzyldimethylalkylammonium chlorides. It was added for its bactericidal properties and until recently was an ingredient in a number of commercially available nebulizer solutions including albuterol, fenoterol, metaproterenol (orciprenaline), beclomethasone dipropionate, and ipratropium bromide. However, this use was not preceded by safety studies examining its effects when inhaled by asthmatics, and ignored in vitro studies that suggested that it would have the potential to cause an adverse airways response.

In Vitro Studies

Benzalkonium chloride has complex activities against rat serosal mast cells in vitro.[14] In concentrations between 1 and 3 μg/ml it inhibits histamine release induced by polyamines such as 48/80, bradykinin, and substance P, but not that caused by antigens, ionophores, monoamines, and detergents. However, at concentrations greater than 5 μg/ml BAC causes histamine release itself, releasing in excess of 90% of the histamine content at a concentration of 30 μg/ml. This concentration is equivalent to the minimum recommended (25 μg/ml) for the use of BAC as a disinfectant,[15] suggesting that the effect could be related to the surfactant properties of the hydrophobic and cationic groups of the molecule. This mechanism is also consistent with the observation that heat inactivation of the mast cells does not prevent the histamine release.[14] Further work in rat serosal mast cells showed that BAC in a concentration of 1.0 μg/ml may enhance IgE-dependent release of the preformed mediator 5-hydroxytryptamine.[16]

In Vivo Studies

Initial experiments on the airway effects of inhaled BAC involved six asthmatic subjects who developed paradoxic bronchoconstriction after inhaling a bronchodilator (Atrovent) nebulizer solution containing BAC.[7] Inhalation of increasing concentrations of BAC 0.125–5.0 mg/ml produced dose-dependent bronchoconstriction that persisted for longer than 60 minutes. The cumulative geometric mean concentration of BAC provoking a 20% fall in forced expiratory volume in 1 second ($PC_{20}FEV_1$) was 0.30 mg/ml (range 0.13–2.0 mg/ml).

In a study of patients with mild atopic asthma who were not selected on the basis of a history of paradoxic bronchoconstriction with nebulizer solutions, inhalation of increasing concentrations of BAC nebulizer solution caused concentration-related falls in FEV_1 in all 12 subjects.[17] The geometric mean $PC_{20}FEV_1$ for BAC was 4.0 mg/ml (range 0.9–24.0 mg/ml), compared with 0.6 mg/ml for histamine (range 0.1–3.9 mg/ml). The slopes of the concentration-response curves with BAC and histamine did not significantly depart from parallel. Based on these results it could be estimated that histamine was about 7.4 times more potent as a bronchoconstrictor agonist than BAC on a mass basis.

In a similar group of nine subjects with mild atopic asthma,[18] the geometric mean $PC_{20}FEV_1$

for BAC was 5.0 mg/ml (range 0.5–19.5 mg/ml). This response was reproducible, with a repeat dose-response challenge in the same subjects resulting in a mean $PC_{20}FEV_1$ of 2.8 mg/ml (range 0.4–15.6 mg/ml). Patients most sensitive to the bronchoconstrictor effects of BAC were those with severe asthma, as determined by marked bronchial hyperresponsiveness.

The relationship between airway sensitivity to inhaled BAC and predisposition to airway hyperresponsiveness was investigated in adults with asthma.[19] Of the 28 subjects, 17 (61%) developed marked bronchoconstriction with inhalation of BAC, and their recovery was slow. The amount of BAC that caused bronchoconstriction was about 300 µg, similar to that contained in a 2.5-mg dose of albuterol nebulizer solution from the screw-cap product currently available in the United States. Inhalation of BAC also enhanced the response to inhaled histamine delivered 1 hour later. The clinical implication of this observation was that inhalation of BAC could temporarily enhance nonspecific bronchial reactivity, thereby making an asthmatic patient more susceptible to developing bronchoconstriction in response to provoking stimuli.

In these studies, the inhibitory effects of potent pharmacologic agents provided evidence that BAC-induced bronchoconstriction results from a combination of mast cell activation and stimulation of peripheral and central neural pathways.

Clinical Relevance

The possibility that BAC in nebulizer solutions may lead to either reduced bronchodilator efficacy or paradoxic bronchoconstriction was investigated in a series of studies and case reports of ipratropium bromide and albuterol nebulizer solutions.

Ipratropium Bromide

There is strong evidence that BAC in commercially available Atrovent nebulizer solution influences airways response. A series of studies identified that inhalation of Atrovent containing both BAC 0.25 mg/ml and edetate disodium (EDTA) 0.5 mg/ml by asthmatic subjects may cause marked bronchoconstriction, and that their exclusion results in a significantly greater bronchodilator effect.[7, 20] For example, in an unselected group of 22 adults with stable asthma,[7] six subjects developed bronchoconstriction after inhaling 4 ml (1.0 mg) of Atrovent, with a mean fall in FEV_1 of 35% at 2 minutes after inhalation (Figure 1). When the six subjects inhaled 4 ml (1.0 mg) preservative-free ipratropium bromide solution, all showed appropriate bronchodilation, with the mean FEV_1 increasing to 12% from baseline at 2 minutes.

A double-blind, randomized clinical trial in 30 adult asthmatics documented a fall in FEV_1 greater than 20% of baseline in 5 patients (17%) receiving the preservative-containing Atrovent, but none in those receiving 2 ml (0.5 mg) of the preservative-free ipratropium bromide solution.[20] Inhalation of preservative-free solution resulted in more rapid and greater overall bronchodilation than inhalation of Atrovent (Figure 2). It is likely that BAC was responsible for the bronchoconstriction associated with Atrovent, as the concentration (0.25 mg/ml) was within the range that causes bronchoconstriction when inhaled by asthmatic subjects, in contrast to EDTA (0.5 mg/ml), which is about one-tenth as

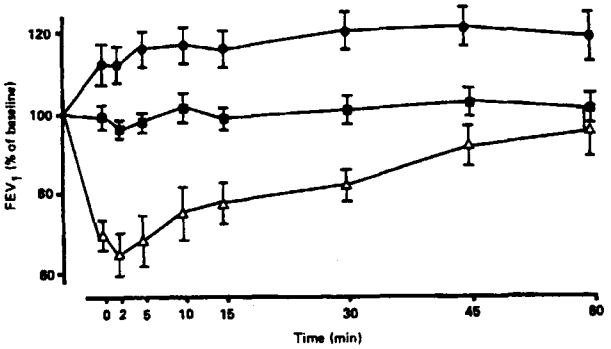

Figure 1. Changes in airway caliber after inhalation of nebulised Atrovent (Δ), preservative-free ipratropium bromide (●) and saline (■) in the six asthmatic subjects in whom the FEV_1 fell more than 20% after inhalation of 4-ml solution of nebulized Atrovent. Each point represents the mean FEV_1 expressed as percentage of baseline, and each bar the SEM. From reference 7.

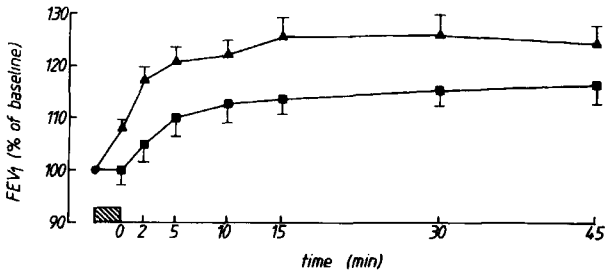

Figure 2. Effect of Atrovent (■) and preservative-free ipratropium bromide (▲) on airway caliber in 30 subjects. Each point represents the mean FEV_1 expressed as percentage of baseline, and each bar the SEM. From reference 20.

potent as a bronchoconstrictor agent.

In a similar study in children with mild asthma, 1 ml of ipratropium bromide nebulizer solution containing BAC and EDTA resulted in a small, insignificant reduction in bronchodilation, compared with the preservative-free solution.[21] This finding is not inconsistent with adult studies in which higher doses of preservatives were administered to patients with more severe asthma, as the bronchoconstrictor response to both BAC and EDTA is dose dependent, and in the case of BAC, is greater in subjects with markedly increased bronchial hyperresponsiveness.

Albuterol

Only one controlled study has examined the effect of BAC (concentration 0.1 mg/ml) on the bronchodilator response resulting from a single dose of albuterol nebulizer solution.[22] Twenty-two patients with moderately severe asthma (baseline predicted FEV_1 43–91%) came to the laboratory on two occasions to inhale 2.5 ml albuterol nebulizer solution (albuterol 1.0 mg/ml) with or without BAC 0.1 mg/ml according to a double-blind protocol. Paradoxic bronchoconstriction, defined as a fall in FEV_1 greater than 5% of baseline, did not occur in any subject after either treatment. There was no significant difference in airways response between the solutions. Possible reasons for this difference in effect of BAC in albuterol or ipratropium bromide solution include its lower concentration in the albuterol solution (0.1 vs 0.25 mg/ml), absence of EDTA in the albuterol solution, and greater potency and more rapid onset of bronchodilator action of albuterol.

This study is relevant to the administration of single doses of albuterol nebulizer solution only, rather than repeat administration, which would occur in the treatment of a severe asthma attack. International consensus guidelines[23] recommend that albuterol be administered initially at a dosage of 2.5–5.0 mg every 20 minutes and then hourly, or even continuous nebulization, in the treatment of severe asthma in a hospital-based emergency department. To our knowledge no studies have examined the effects of BAC in albuterol nebulizer solution when administered repeatedly in high doses in severe asthma. However, at least two case reports in the literature provide evidence for an association between repeated use of albuterol nebulizer solution containing BAC and the occurrence of paradoxic bronchoconstriction.

Patient No. 1. A 64-year-old man experienced a respiratory arrest after nebulization with albuterol and ipratropium bromide solutions containing BAC in concentrations of 0.1 and 0.25 mg/ml, respectively.[24] It is possible that the ipratropium bromide solution also contained EDTA, but this was not stated. The patient, who had severe chronic obstructive airway disease, complained of increased breathlessness after each nebulized treatment with albuterol 1 ml mixed in ipratropium bromide 2 ml. The deterioration was confirmed with lung function measurements, with for example, pretreatment FEV_1 falling from 0.58 to 0.49 L 30 minutes after treatment. The patient suffered a respiratory arrest 30 minutes after nebulizer therapy. This was attributed to the effect of BAC in the solutions in view of the time course, the amount of BAC present in the solutions, and the lack of this reaction to drugs when administered by metered-dose inhalation. The authors calculated that the patient was exposed to a dose of 0.6 mg of BAC/treatment, compared with doses of less than 0.2 mg shown to drop FEV_1 by 20% of baseline in asthmatic patients.[7, 19]

Patient No. 2. A 16-month-old girl was admitted to intensive care with severe respiratory distress and given albuterol containing BAC by nebulization every 30 minutes and then hourly.[25] By 12 hours after admission her condition began to deteriorate, and while preparations were made for intubation and ventilation, she was administered preservative-free terbutaline 3 mg with a favorable response. When albuterol nebulizer solution was administered again, it again resulted in significant deterioration with documentation of a drop in arterial oxygen saturation. Again, a single treatment with terbutaline by inhalation resulted in complete clearing. The authors concluded that the paradoxic bronchoconstriction was highly suggestive of an adverse reaction to BAC in the albuterol nebulizer solution. It was evident from this report that it would be difficult to recognize deterioration due to a bronchodilator nebulizer solution in such circumstances, as lack of response to a high-dose bronchodilator is one of the characteristic features of life-threatening asthma.

Complementing this second case report are two recent studies in infants with asthma showing that paradoxic bronchoconstriction after albuterol nebulizer solution containing BAC is not uncommon.[26, 27] In both studies, adminis-

tration of nebulized albuterol solution containing BAC caused acute deterioration in lung function. Although the authors raised a number of possibilities to account for the deterioration, including changes in osmolality during the process of nebulization and a reduction in airway smooth muscle tone leading to a change in airway compliance, the potential adverse effects of BAC were not excluded.

Thus the available evidence suggests that although the presence of BAC in an albuterol nebulizer solution is unlikely to affect the bronchodilator response after a single dose, it may cause paradoxic bronchoconstriction with repeat administration in patients with severe asthma, a response that would be difficult to detect clinically. Clinical studies are urgently required to resolve this issue.

Sensitization

In addition to short-term adverse airway effects of BAC, the possibility also exists that sensitization to this agent may occur with repeated exposure. The initial report of possible sensitization to BAC came from a study of 113 workers in the pharmaceutical cosmetic industry with occupational exposure to quaternary ammonium salts such as BAC.[28] Among these workers, 17 had positive skin patch tests; 10 of the 17 developed eczema, conjunctivitis, or rhinitis. Although no cases of occupational asthma were reported, a case of presumed occupational asthma due to BAC was described by others.

Patient No. 1. A 37-year-old nonsmoker initially developed a dry cough and rhinorrhea, then experienced her first attack of asthma about 4 months after starting work in a hospital laundry.[29] At first, because of the suspected role of trichloroethylene used in the dry-cleaning process, she was transferred to the wards as an aide, but her asthma did not regress. Both in the laundry and in the ward, the patient used disinfectant products based on BAC for cleaning floors. Her condition worsened, and results of investigations included positive patch tests to BAC at 4 hours and a positive bronchial provocation test to the agent. In the latter test, inhalation of BAC in a concentration of 100 mg/ml led to a maximum 35% fall in peak expiratory flow rate (PEFR) after 15 minutes. This airways response was prolonged, as despite initial reversal with 200 mg albuterol, the PEFR again fell by 26% after 3 hours. In contrast, bronchial provocation with trichloroethylene did not cause a significant airway response; also skin patch tests to this and other agents were negative. A diagnosis of occupational asthma due to BAC was made, although the airway response to BAC may have reflected the degree of the patient's bronchial hyperresponsiveness, rather than specific sensitization to BAC.

Anaphylactoid Reaction

Anaphylactic reaction, including marked flushing, dizziness, cough, and itching of the face and neck, occurred after treatment with albuterol nebulizer solution including BAC in a concentration of 0.1 mg/ml.[30] Investigations indicated that this response was due to BAC in the solution. Indeed,the patient experienced a more severe systemic reaction with angioedema after intradermal testing with BAC.

EDTA

Edetic acid is a calcium-chelating agent that does not inhibit microbial growth. It is present in some nebulizer solutions to chelate metallic ions and thus prevent solution discoloration. As with BAC, its presence in commercially available nebulizer solutions was not based on research investigating its safety.

In Vivo Studies

Animal Models

In anesthetized Basenji-Greyhound (BG) dogs with hyperreactive airways, a 5-minute challenge with aerosols of EDTA resulted in greater than 4-fold increase in pulmonary resistance and 2-fold reduction in dynamic compliance.[31] Peak response occurred after 5 minutes, with continued effect persisting for at least 25 minutes. Although less marked in comparison, airway constriction was also induced by EDTA in pure-bred Basenji dogs that lack airway hyperresponsiveness.[32]

These studies showed that the airway effect of EDTA is due to calcium chelation and not to either the acidity or osmolality of solution. Although the precise mechanisms by which calcium chelation induces bronchoconstriction in BG dogs is unclear, it may involve mediator release, since citric acid-induced bronchoconstriction is blocked by FPL 55712,[33] is attenuated by sodium cromoglycate,[34] and is associated with probable release into the plasma of LTD_4.[33, 34] Vagally mediated reflexes are not involved, since atropine is ineffective in

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