Nebulized Bacteriostatic Saline as a Cause of Bronchitis

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Background. The purpose of this study was to determine whether nebulized bacteriostatic saline, which contains the preservative benzyl alcohol, is an irritant to the tracheobronchial mucosa in healthy adults.

Methods. A randomized, double-blind, placebo-controlled study was conducted with 10 healthy adults who inhaled 3 mL of either bacteriostatic saline or saline placebo by nebulizer four times a day for 2 weeks. Pulmonary function tests and bronchoscopy with biopsy were performed immediately before and after the 2-week nebulization period.

Results. Nine of 10 volunteers were compliant with the study protocol. Four of five volunteers who used nebulized bacteriostatic saline developed bronchitic symptoms and had bronchoscopic evidence of bronchitis. The fifth remained healthy. Four volunteers used nebulized saline (placebo). Two of these four became ill, one with a much more severe bronchitis than any of the bacteriostatic saline volunteers, and one with pharyngitis. Bronchoscopic biopsies showed a lymphocytic mucosal infiltrate in those who became ill while using nebulized bacteriostatic saline and a polymorphonuclear mucosal infiltrate in those who became ill while using nebulized saline placebo.

Conclusions. Nebulization of bacteriostatic saline, containing benzyl alcohol as its preservative, causes bronchitis in healthy adults. Even nebulization of sterile saline may be associated with bronchitis and pharyngitis. Physicians who prescribe nebulized medications must pay close attention to the bronchodilator diluent.

Key words. Bacteriostatic saline; bronchitis; nebulizers and vaporizers; benzyl alcohols; preservatives, pharmaceutical.

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Nebulization of medications has revolutionized pulmonary care in the past decade. It is now common for adult and pediatric pulmonary patients to have portable handheld nebulizer equipment at home.[1] While this modality has allowed many patients to lead more normal lives, it is increasingly evident that nebulization has risks.

Some specific nebulizer-related problems have been reported. Nebulization of hypotonic solutions can cause paradoxical bronchospasm.[2] Sodium metabisulfite and benzalkonium chloride, used as preservatives in many nebulizer medications, can also cause bronchospasm.[3-5] Multidose bottles of bronchodilator that contain preservatives can become bacterially contaminated during their use if meticulous sterile technique is not used while measuring medication.[6] The nebulizer cup and mouthpiece may themselves harbor gram-negative bacilli and other respiratory pathogens.[6-10] Rinsing the nebulizer cup with tap water may contaminate it with waterborne pathogens such as *Legionella*.[11] One of the authors of the current study has previously reported the case of an adult patient with recurrent bouts of bronchitis and hemoptysis that were associated with the use of bacteriostatic saline as nebulizer diluent.[12]

Bacteriostatic saline contains benzyl alcohol (BA) as its preservative. Commercially available bacteriostatic saline solutions contain 9 mg of BA and 9 mg of sodium chloride per milliliter. Benzyl alcohol is a well-known toxin. It has caused fatal metabolic acidosis when administered parenterally to preterm neonates.[13] Temporary and permanent paralyses have resulted from inadvertent administration of intrathecal bacteriostatic saline.[14] Benzyl alcohol is a known topical sensitizer.[15] In animal toxicologic studies of parenteral BA, neurotoxicity, hepatoxicity, and nephrotoxicity have all been seen.[16] In these

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animal studies, the specific lesion of peribronchial lymphoid follicular hyperplasia was noted.[16]

The index patient previously reported by one of the authors (R.D.R.) had chronic obstructive pulmonary disease.[12] He periodically used nebulized albuterol from a multidose vial "diluted in 2 mL of normal saline" for dyspnea. The patient had used this therapy intermittently for approximately 6 years. Eighteen months before his nebulizer-induced bronchitis and hemoptysis was recognized, the patient had changed to a new pharmacist. The pharmacist dispensed bacteriostatic saline as the albuterol diluent in a 30-mL multiple-dose vial. The patient experienced three episodes of severe bronchitis with hemoptysis, all beginning after at least 1½ weeks of continuous four-times-a-day nebulizations. Bronchoscopy during one of these episodes showed a curious pattern of inflammation: worse in the proximal trachea and less pronounced in the segmental bronchi. No further bouts of bronchitis were seen for 2½ years, during which preservative-free saline for nebulization (BronchoSaline, Blairex Laboratories, Columbus, Ind) was substituted as a diluent for the albuterol.[12]

After reporting this case, one of the authors (R.D.R.) attempted to get the manufacturers to place a warning label on bacteriostatic saline vials stating "Not for inhalation." The vials already carry a "For drug-diluent use only, not for use in newborns" warning. This suggested new warning was initially rebuffed by the manufacturers, who questioned whether the patient's reaction was idiosyncratic. At the time of this study, our index patient had a negative skin-patch test for sensitivity to benzyl alcohol.

To determine how widespread a practice it is to dispense bacteriostatic saline for nebulizer diluent, 71 Cincinnati pharmacists were polled by telephone. They were randomly chosen from the yellow-page listings of pharmacies and included both chain and private pharmacies. The pharmacists were asked which saline product they would dispense if the "sig:" on an albuterol nebulizer solution prescription read "dilute in 3 mL normal saline."

A wide variety of preferences were found. The majority (55%) would dispense BronchoSaline. Eighteen (25%) responded that they would dispense plastic unit-dose ampules of sterile saline ("pillows") that are intended for nebulization and widely used in hospitals. These are the only two saline products available in the United States that are indicated for nebulization.

The remaining pharmacists recommended products that can become contaminated during use or are otherwise potentially dangerous. Eight reported that they would dispense a 1000-mL bottle of preservative-free saline intended for irrigation and a syringe to measure out the diluent aliquot. Three reported using this same product but pouring it into a 4-oz bottle, citing worries over contamination of such a large volume. One pharmacist reported dispensing a 500-mL glass bottle containing intravenous saline. Another pharmacist stated that he makes his own sterile saline solution using distilled water and sodium chloride tablets. One mentioned another pharmacist who dispenses a saline solution intended for use with contact lenses. This type of saline solution is distributed in sealed, pressurized, multidose canisters and is preservative-free, but contains buffers, the tracheobronchial effect of which is unknown. One pharmacist mentioned that he occasionally dispenses sterile water for irrigation, incorrectly stating that this product does not need a prescription. One pharmacist was found to dispense 30-mL vials of bacteriostatic saline.

We undertook this study to determine whether bacteriostatic saline is a nonspecific irritant to the tracheobronchial mucosa. We theorized that if this association could be proven, it would verify the need for an inhalation warning label on bacteriostatic saline vials.

Methods

Ten healthy lifetime nonsmoking adult volunteers were recruited from a local church population. None had a history of respiratory disease. They were told to expect a 50:50 chance of developing bronchitis during the study. Written informed consent was obtained. Volunteers were prescreened by means of a complete history and physical examination, CBC, biochemical profile, Westergren erythrocyte sedimentation rate, and urinalysis. Each volunteer was skin-patch tested for sensitivity to 5% BA, USP (United States Pharmacopeia), in liquid petrolatum saturating a Whatman 5-mm filter paper disk, held in place in a Finn chamber on Scanpor tape.[17] All volunteers had a negative patch-test reaction at 48 hours. Pulmonary function testing (PFT) including vital capacity, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow, and forced expiratory flow between 25% and 75% exhalation were performed using a Compact spirometer (model 42.000, Vitalograph Inc, Lenexa, Kan). Each volunteer had PFTs within normal range for his or her age and size. Flexible fiberoptic bronchoscopy using an Olympus BF-P20D bronchoscope (Olympus America, Inc, Lake Success, NY) was performed on all volunteers immediately before the study to document normal appearance of the tracheal and bronchial mucosa. Permanent pictures were obtained during bronchoscopy using an Olympus OTV-F2 endoscopy imaging system. Biopsies were obtained from the carina to document microscopically normal mucosa.

Ten numbered but otherwise unlabeled canisters were provided by Blairex Laboratories. Five of these con

tained preservative-free sterile saline for nebulization (BronchoSaline) in its usual but unlabeled delivery system, a pressurized aluminum canister with a one-way valve mechanism that delivers 1 mL per actuation. These were sterilized by gamma irradiation, the manner customarily used for commercially available BronchoSaline. The other five canisters contained bacteriostatic saline (Abbott Laboratories, Abbott Park, Ill), repackaged in an identical delivery system. To avoid concerns over radiation-induced alteration of the BA, empty cannisters were gamma-irradiated, bacteriostatic saline was placed inside using sterile technique and pressurization, and the canisters were sealed in a sterile fashion.

Sterility of the solutions was documented by Blairex using USP standard methods. One extra container of each solution was sent to Scientific Associates, Inc, St. Louis, Mo, for destructive testing. The entire contents of each bottle were drawn through a 0.45-micron filter to trap any organisms. The filter was divided using sterile technique and incubated in various liquid media for 14 days. No growth of aerobic or anaerobic bacteria, yeasts, or molds was seen from sample containers of either solution.

Each volunteer chose a canister by drawing a number from a hat. The investigators and volunteers were unaware of each canister's content during the study.

Immediately after the first bronchoscopy, each volunteer was provided with an Aerosol Two compressor and Custom nebulizer (Medical Industries America, Inc, Adel, Iowa) and instructed in its use and cleaning. Each volunteer inhaled 3 mL of solution four times a day for 2 weeks using the nebulizer. They were instructed to report any problems or respiratory symptoms to the investigators.

At the end of 2 weeks, or if respiratory symptoms developed, each volunteer had a repeat bronchoscopy and another carinal biopsy was obtained. Permanent bronchoscopy pictures were obtained again. Pulmonary function tests were repeated just before the second bronchoscopy.

Solution canisters were collected from the volunteers at the completion of the study. Before and after weights were compared to document compliance with the nebulization regimen. Aliquots from each canister were analyzed for BA content to recheck the bottle numbering code. Biopsy specimens were mainstreamed into a community hospital pathology department with a sham diagnosis on the request form to blind the pathologists to the study conditions. The study protocol was approved by the Institutional Review Board of Mercy Hospital Anderson, Cincinnati, Ohio, where the bronchoscopies were performed.

Results

Nine of the 10 volunteers completed the study protocol. One volunteer was noncompliant, doing only 12 nebulizations during the 2-week study period. Bottle weights documented that the other nine volunteers averaged 49.2 nebulizations, with a range of 38 to 68.

Six volunteers became clinically ill, five with bronchitic symptoms (chest tightness, wheezing, and coughing) and one with pharyngitis. The volunteer with pharyngitis became symptomatic on day 7. Examination at that time showed an erythematous pharynx and uvular edema but no exudate. His nebulization treatment was discontinued on day 10, and he had a repeat bronchoscopy on day 11. The other eight volunteers completed the entire 2 weeks on the nebulization regimen. One of the ill participants, volunteer 9, had such a severe cough that repeat PFTs could not be obtained. A summary of the data from the nine participants who completed the study is presented in the Table.

Four of the five volunteers who used nebulized bacteriostatic saline developed respiratory symptoms, including tightness in the chest, wheezing, coughing, and rhinorrhea. Bronchoscopy in all four showed erythema and edema of the tracheobronchial mucosa, which was generally worse in the proximal trachea. Figure 1 shows before and after bronchoscopic views of the carina in volunteer 3. Some BA-exposed volunteers showed metaplasia, denudation of cilia, and mucosal lymphocytic infiltration on bronchoscopic carinal biopsy. (Technical problems limited our biopsies of their friable mucosa. Adequate specimens were not obtained from all volunteers.) The fifth volunteer who used nebulized bacteriostatic saline remained asymptomatic but had lymphocytic infiltration on biopsy.

Two of the four volunteers who used nebulized saline placebo remained asymptomatic and two became clinically ill. The most ill participant was volunteer 9. On day 11, she developed coryza. On day 13, she developed chest tightness, sputum production, and a severe cough. Unlike those who had used nebulized bacteriostatic saline and became ill, she showed mucosal polymorphonuclear cell infiltration on bronchoscopic biopsy. Volunteer 8 used nebulized saline and developed pharyngitis. He had no lower respiratory tract symptoms but did have some tracheal erythema at bronchoscopy. His carinal biopsy showed polymorphonuclear cell infiltration. Bronchoscopic cultures selectively obtained in volunteers 1 and 9 grew no pathogens. Destructive testing of the remaining saline solution in canisters from volunteers 8 and 9 showed no pathogens.

The Table shows FEV_1 and FVC data, expressed as a percentage of expected normal for the volunteer. There

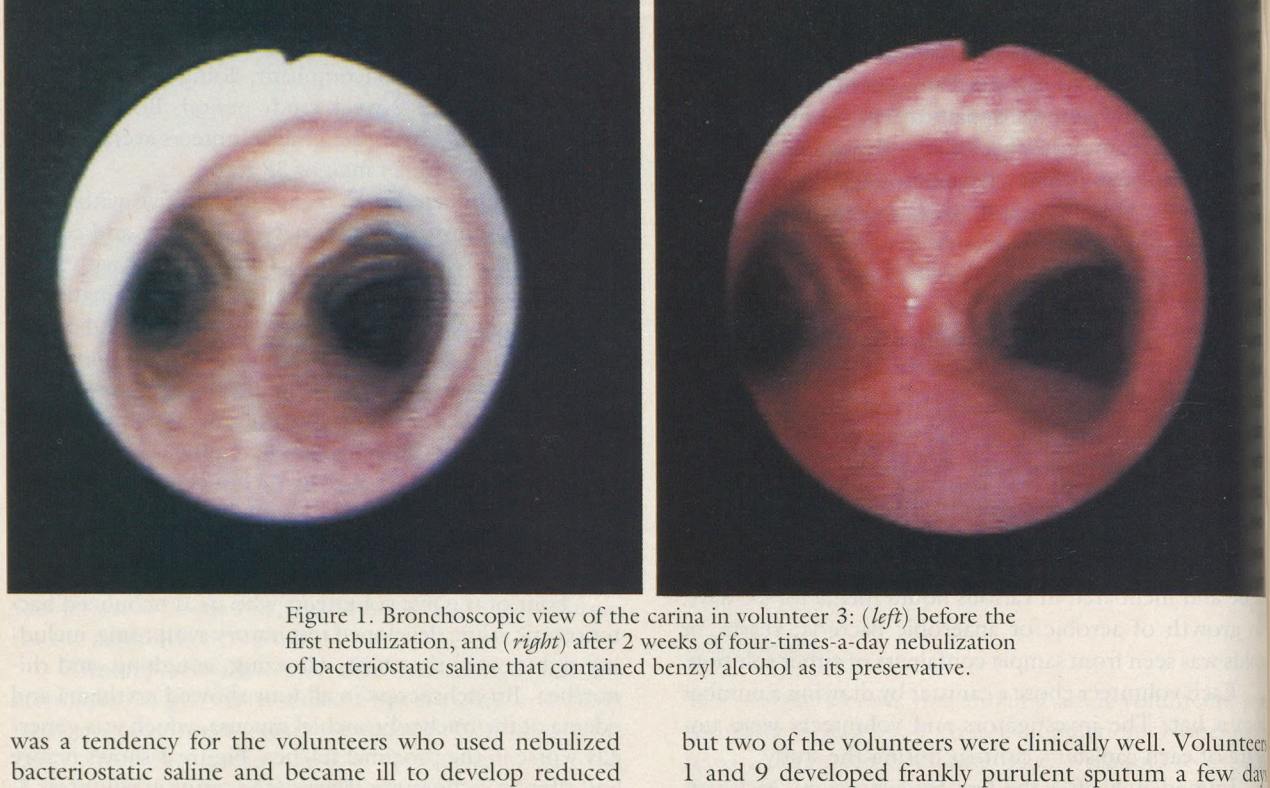

Figure 1. Bronchoscopic view of the carina in volunteer 3: (*left*) before the first nebulization, and (*right*) after 2 weeks of four-times-a-day nebulization of bacteriostatic saline that contained benzyl alcohol as its preservative.

was a tendency for the volunteers who used nebulized bacteriostatic saline and became ill to develop reduced FVC. Because of the small sample size, this trend does not reach statistical significance. FEV_1 data show that these normal volunteers did not develop significant bronchospasm when exposed to BA, although three of the five developed either chest tightness or wheezing, suggesting some degree of airway obstruction.

Within 2 to 3 days of discontinuing nebulization, all but two of the volunteers were clinically well. Volunteer 1 and 9 developed frankly purulent sputum a few day after the study that required antibiotic treatment.

Discussion

Our findings suggest that nebulization of bacteriostati saline containing benzyl alcohol as a preservative cause

Table. Results of Nebulization Study Involving 9 Healthy Adults Who Used a Nebulizer with Either Bacteriostatic Saline Containing Benzyl Alcohol or Saline Placebo Four Times a Day for 2 Weeks

Patient Volunteer No.	Age	Sex	Pre-FEV_1	Initial Post-FEV_1	Final Post-FEV_1	Pre-FVC	Post-FVC	Symptoms Developed	Post-Bronchoscopic Findings	Biopsy
Bacteriostatic saline (BA) nebulization group										
1	29	M	90	91	92	108	97	C,T,W	T,B,R	M,LC,L
2	59	M	103	101	90	107	95	C,R	T	US
3	38	F	103	101	94	107	94	W,R	T,B	M,LC,L
4	33	F	102	100	100	103	102	C,T,R	T,B	US
5	44	M	91	90	92	87	90	None	NL	L
Saline placebo nebulization group										
6	60	F	102	101	100	100	96	None	NL	NL
7	39	F	105	106	105	111	109	None	NL	NL
8	59	M	89	89	87	86	94	P	T	LC,P
9	59	F	88	93	-	96	-	C,T,R	T,B	M,LC,P

FEV_1 denotes forced expiratory volume in 1 second, as a percentage of expected normal. Initial post-FEV_1 is defined as FEV_1 immediately after first nebulization. Final post-FEV is FEV_1 at end of study. FVC denotes forced vital capacity, as a percentage of expected normal. Symptoms developed: C denotes cough; T, tightness in chest; W, wheeze; R, rhinorrho P, pharyngitis. Post-bronchoscopic findings: T denotes tracheitis, B, bronchitis; R, rhinitis; NL, normal. (On bronchoscopic findings, inflammation was noted only if erythema an edema were observed.) Biopsy (post 14-day nebulization): M denotes metaplasia of mucosa; LC, loss of cilia; L, lymphocytic infiltration of mucosa; P, polymorphonuclear infiltrati of mucosa; NL, normal; US, unsatisfactory for evaluation.

bronchitis in healthy adults. This finding is of great importance to all clinicians who prescribe nebulizer therapy. Bronchitis may result if the prescribing physician fails to specify the saline product to use as nebulizer diluent. Since sharing our data with the United States Pharmacopeial Convention, a new USP warning label has been mandated on all vials of bacteriostatic saline stating "Not for Inhalation."

We suspect that BA is a nonspecific irritant to bronchial mucosa. All our volunteers were prescreened with BA skin-patch testing to exclude prior sensitization as a reason for their bronchitis. Our index patient and the four volunteers who developed bronchitis as a result of nebulized bacteriostatic saline had a tendency for the tracheal mucosa to appear more inflamed in the subglottic area than in the mainstem and segmental bronchi. Radiolabeled studies have shown that aerosolized droplet deposition diminishes as airways narrow.[18,19] We therefore suspect that the areas that became most erythematous had the most BA deposition, explaining the curious pattern of inflammation.

Two results of this study require explanation. First, volunteer 5 was treated with nebulized bacteriostatic saline but did not develop symptomatic bronchitis, although he showed lymphocytic mucosal infiltration on carinal biopsy. He is a toxicologist who works extensively with organic alcohols, although he states he has never been exposed to BA.

Second, that two volunteers became ill while using the nebulized saline (the placebo) was an unexpected finding. Both of them had illnesses that were clinically different from the four BA-exposed volunteers who became ill. This study was conducted during February, unfortunately a prominent time for the development of many respiratory illnesses. Volunteer 8's illness was primarily pharyngitis and volunteer 9 developed a typical viral upper respiratory tract infection that progressed to acute bronchitis. Bronchoscopic cultures from volunteer 9 grew no pathogens. Both volunteers showed polymorphonuclear cell infiltrations on their postnebulization carinal biopsies, unlike the BA-exposed volunteers who became ill. Aliquots of solution from their bottles were reanalyzed after the study and found to be sterile. We suspect that one of them may have had viral pharyngitis and viral upper respiratory tract infection and the other, bronchitis.

Recent reports suggest that nebulizer cups can rapidly become colonized with gram-negative bacteria.[6–11] Contamination by this may be another plausible explanation for infection in these two volunteers. We presume that the BA-exposed volunteers had less potential for bacterial contamination of their nebulizer setups than did those who used a nebulizer with preservative-free saline. Unfortunately, we were not aware of this potential for rapid bacterial colonization at the time of the study and did not culture our volunteers' nebulizer cups. Not expecting infectious complications, we also did not do bronchoscopic cultures on all volunteers. Bacteriologic studies of the volunteers' solution canisters showed that they were not a source of contamination.

We instructed the volunteers to treat the inside of the nebulizer cup and mouthpiece as a sterile environment and to "wash it in hot soapy water, rinse with hot water, and air dry the nebulizer cup and mouth piece once a day; more frequently if it came in contact with anything." Unfortunately, we did not specify cleaning protocols that are now becoming standard practice: using sterile fluids for rinsing the nebulizer cup, a daily 15-minute vinegar soak of the nebulizer cup, and completely drying the setup between nebulizations.

Our study suggests three points that are important to clinicians. First, bacteriostatic saline should not be used as a nebulizer diluent since it appears that benzyl alcohol is an irritant to the tracheobronchial mucosa.

Second, it is important to specify the exact saline product that is to be dispensed as nebulizer diluent. There are only three safe ways of prescribing nebulizer medications. Many bronchodilator medications are available in prediluted unit-dose form. These cost the most but eliminate contamination worries. The other two less-expensive options are a concentrated medication in its dropper bottle and dilution with either unit-dose saline "pillows" or with BronchoSaline.

Average wholesale price (AWP) data in July 1994 show that prediluted Proventil costs $1.42 per dose (purchased in boxes of 25), Proventil concentrate diluted with "pillows" ranges between 55 and 71 cents per dose depending on "pillow" manufacturer (Proventil concentrate in a 20-mL bottle has 40 doses, each costing 39 cents; "pillows" range in price from $16.25 to $31.82 for boxes of 100), and Proventil concentrate diluted in BronchoSaline costs 49 cents per dose (BronchoSaline is available in a 240 mL container at an AWP of $6.04; this contains 60 doses, for a cost of 10 cents per dose). Retail prices on all these options are somewhat higher.

Third, from a bacteriologic standpoint, nebulization itself may be a potentially dangerous practice. There is a risk of deep respiratory deposition of anything that comes in contact with the nebulizer setup. Meticulous detail to sterile technique and continual decontamination and drying of the nebulizer setup are required to ensure that home nebulization is a safe practice.

The current preferred practice to minimize nebulizer contamination appears to be: (1) air drying the nebulizer cup after each use by blowing air through with the com-

pressor,[8] (2) never washing the tubing between the compressor and nebulizer cup,[8] (3) periodically soaking the nebulizer cup in vinegar for 15 minutes,[6,7] and (4) using only sterile solutions to rinse the nebulizer cup before drying.[11] The responsibility for ensuring that patients are taught proper sterile technique and decontamination procedures rests squarely with the prescribing physician.

Conclusions

Our small randomized, double-blind, placebo-controlled study suggests that nebulized bacteriostatic saline that contains benzyl alcohol as its preservative causes bronchitis in healthy adult volunteers.

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