NOTE

Mixing and compatibility guide for commonly used aerosolized medications

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Purpose. A mixing and compatibility guide for commonly used aerosolized medications was developed.

Summary. Compatibility guides for injectable drugs are available as a reference for pharmacists, nurses, and medical personnel. These charts are commonly used in hospitals and other health care institutions and provide a quick, easy reference for compatibility of frequently used intravenous medications. Respiratory therapists are frequently directed to administer various aerosolized medications and are often faced with the challenge of uncertain compatibility of these drugs when mixed together. However, there appear to be limited data regarding the compatibility of these aerosolized admixtures. After a careful review of the literature, a compatibility chart was developed that should provide significant value to pharmacists, nurses, and respiratory therapists who administer aerosolized medications. The authors of a recently published evaluation of the compatibility of common inhalation solutions summarized their findings in a concise table. This table served as a template to develop a more comprehensive mixing and compatibility guide in the form of an easy-to-use reference chart, which includes additional agents, compatibility references on the chart, and compatibility information for pharmacists, nurses, physicians, and respiratory therapists.

Conclusion. A compatibility guide for aerosolized medications was developed for use by staff who administer these agents.

Index terms: Aerosols; Compounding; Guidelines; Incompatibilities; Stability

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Compatibility references of i.v. medications provide easily accessible information to guide the safe administration of parenteral therapy.[1,2] On the other hand, compatibility information for inhaled aerosolized medications is limited.[3,4]

A compatibility chart can potentially save time by answering the most common questions about admixtures. A chart can provide a quick and easy reference for medical personnel about compatibility of frequently used i.v. medications, including chemotherapy agents, antibiotics, vasopressors, and other drugs.

Locating this information can be very challenging, as it often can be found only in the primary literature. Trials are heterogeneous, and results can be confusing, even contradictory.[3] A careful review of which inhalation admixtures were tested and the methods used for testing is critical when reading these published trials.

Trissel's Stability of Compounded Formulations[5] and Trissel's 2 Clinical Pharmaceutics Database[6] provide comprehensive data on several aerosolized drugs, including compatibility and stability data for various admixtures. These references are relatively unfamiliar to nurses, respiratory therapists, and physicians. There is no aerosolized admixture counterpart to the parenteral i.v. admixture chart.

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Figure 1. Compatibility guide for commonly used inhalation solutions and suspensions. Dark green shading with corresponding letter C indicates that there is evidence in the form of clinical studies confirming the stability and compatibility of the particular admixture. Light green shading with corresponding letter C indicates that there is evidence from manufacturers' reports confirming the stability and compatibility of a particular admixture[3]; in many instances, these studies were unavailable for review and were confirmed either by reference in the package insert or direct communication with the manufacturer. Red shading with corresponding letter X indicates that there is evidence confirming or suggesting that a particular admixture is not compatible. Yellow shading with corresponding letters NI indicates that there is insufficient evidence to evaluate compatibility and should be avoided unless future evidence becomes available. Blue shading with corresponding letters CD indicates that there are conflicting data regarding compatibility of the combination. The following information should be considered when determining the feasibility of preparing drug combinations for inhalation: (1) all admixtures should be prepared from formulations that do not contain preservatives, (2) The *United States Pharmacopeia* requirements state that the particle size of the delivered drug must be carefully controlled and the average diameter must be <5 μm, (3) physical and chemical compatibilities do not describe possible effects on aerodynamic behavior, (4) decreases in temperature can occur in certain nebulizers, and the effect of such decreases on compatibility has not been studied, (5) mixing solutions or suspensions increases total volume, and the relationship between the volume fill, total mass output, and inhaled mass of nebulized drug must be considered, and (6) if admixtures are to be stored, sterility issues must be addressed. References should be consulted to verify drug concentrations are compatible.

	Albuterol	Arformoterol[a]	Epinephrine[b]	Formoterol	Levalbuterol[c]	Metaproterenol[d]	Budesonide	Cromolyn[e]	Ipratropium	Acetylcysteine[f]	Colistimethate[g]	Tobramycin[h]	Sodium Chloride Solutions	Dornase Alfa
Albuterol		NI	NI	NI	NI	NI	C[3]	C[3,i]	C[3,i,j]	NI	C[3,k]	C[3]	NI	X[3]
Arformoterol	NI		NI	NI	NI	NI	C[a]	NI	C[a]	C[a]	NI	NI	NI	X[3]
Epinephrine	NI	NI		NI	NI	NI	NI	C[11]	NI	NI	NI	NI	NI	X[3]
Formoterol	NI	NI	NI		NI	NI	C[13]	NI	NI	NI	NI	NI	NI	X[3]
Levalbuterol	NI	NI	NI	NI		NI	C[3,c]	C[c]	C[c]	NI	NI	NI	NI	X[3]
Metaproterenol	NI	NI	NI	NI	NI		NI	C[11]	C[3]	NI	NI	NI	NI	X[3]
Budesonide	C[3]	C[a]	NI	C[13]	C[c]	NI		C[3,l]	C[3]	C[3]	NI	X[3]	NI	X[3]
Cromolyn	C[3,i]	NI	C[11]	NI	C[c]	C[11]	C[3,l]		C[3,m]	C[3,11]	NI	X[3]	NI	X[3]
Ipratropium	C[3,i,j]	C[a]	NI	NI	C[c]	C[3]	C[3]	C[3,m]		C[14]	NI	C[3]	NI	X[3]
Acetylcysteine	NI	C[a]	NI	NI	NI	NI	C[3]	C[3,11]	C[14]		C[3,n]	NI	NI	X[3]
Colistimethate	C[3,k]	NI	NI	NI	NI	NI	NI	NI	NI	C[3,n]		CD[3]	NI	X[3]
Tobramycin	C[3]	NI	NI	NI	NI	NI	X[3]	X[3]	C[3]	NI	CD[3]		NI	X[3]
Sodium Chloride Solutions	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI		X[3]
Dornase Alfa	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	

[a]No safety and efficacy studies available for admixtures of arformoterol with other drugs; physical and chemical compatibility studies with acetylcysteine, ipratropium, budesonide, and tiotropium have indicated compatibility of concentrations studied (Quon CL, Sepracor, personal communication, 2009 Sep 24).

[b]Epinephrine is readily destroyed by oxidizing agents or alkali (e.g., sodium bicarbonate, halogens, permanganates, chromates, nitrates, nitrites) and salts of easily reducible metals (e.g., iron, copper, zinc).[7]

[c]No safety and efficacy studies available for admixtures of levalbuterol with other drugs; physical and chemical compatibility studies with budesonide, cromolyn, and ipratropium have indicated compatibility of concentrations studied (Quon CL, Sepracor, personal communication, 2009 Sep 24).

[d]No safety and efficacy studies available for admixtures of metaproterenol with other drugs available from manufacturer (Lee S, Dey Laboratories, personal communication, 2009 Sep 24).

[e]Compatibility of cromolyn (Intal, King Pharmaceuticals) with albuterol (Ventolin, GlaxoSmithKline), fenoterol (Berotec, Boehringer Ingelheim), metaproterenol (Alupent, Dey Laboratories), and terbutaline (Bricanyl, AstraZeneca) confirmed by manufacturer.[3]

[f]Acetylcysteine (Mucomyst, Sandoz Pharmaceuticals) has been reported to be compatible with netilmicin or betamethasone.[3] The manufacturer reports that acetylcysteine is incompatible with amphotericin B, tetracyclines, erythromycin, or ampicillin; also incompatible with any oxidizing agent, iodized oil, trypsin, chymotrypsin, and hydrogen peroxide.[8]

[g]Colistimethate sodium (available as an injectable formulation in the United States; dosage expressed in terms of colistin) is not approved for inhalation via a nebulizer; a case of acute respiratory failure and subsequent death of a cystic fibrosis patient who received premixed colistimethate sodium via nebulization has been reported.[9] The prescribing information for a formulation available outside of the United States (Colistin, Grunenthal) states that precipitation may occur in admixtures with other nebulized antibiotics.[3]

[h]Tobramycin solution for oral inhalation should not be diluted or mixed with other drugs in the nebulizer. Based on protocols used in clinical studies evaluating tobramycin solution for oral inhalation in cystic fibrosis patients, it has been recommended that patients receive doses of inhaled bronchodilators first, then dornase alfa, then chest physiotherapy, and then tobramycin.[10]

[i]Admixtures of albuterol, cromolyn, and ipratropium appear to be stable, with ipratropium as the limiting component.[3]

[j]Albuterol and ipratropium are available as a combination solution for nebulization (Duoneb, Dey Laboratories, Napa, CA).

[k]Albuterol containing benzalkonium chloride (1 mL) mixed with 1 mL colistin (Coly-Mycin M Parenteral, 33.3 mg/mL, King Pharmaceuticals) resulted in immediate cloudiness, which was believed to be due to interaction of benzalkonium chloride with colistin (effect on aerodynamics unknown); colistin mixed with preservative-free unit-dose albuterol inhalation solution was chemically stable for one hour.[3] No additional information available from manufacturer (Guinto A, JHP Pharmaceuticals, personal communication, 2009 Sep 24).

[l]Manufacturer of budesonide (Pulmicort, Astra Zeneca GmbH, Wedel, Germany) stated that cloudiness occurred in mixtures of budesonide with cromolyn (Intal), but information is not included in the prescribing information or corroborated by studies.[3]

[m]Prescribing information for ipratropium (Atrovent, Boehringer Ingelheim) states that it should not be mixed with cromolyn because precipitation can occur. It has been reported that cromolyn mixed with ipratropium instantly produced cloudiness, which was attributed to the effect of an unknown excipient in the cromolyn formulation; the manufacturer attributed the cloudiness to benzalkonium chloride in the formulation. However, ipratropium mixed in a nebulizer with cromolyn sodium solution for oral inhalation also has been reported to be stable for one hour.[3]

[n]Acetylcysteine sodium solution (10%) for oral inhalation and colistin 37.5 mg/mL have been reported to be compatible, with immediate use recommended.[3]

Table 1.
Inhaler Device Recommendations for Aerosolized Medications[20-23]

Medication and Concentration	Recommended Inhaler Device	Comments
Albuterol		
Nebulized solution: 0.63 mg/3 mL, 1.25 mg/3 mL, 0.5 mg/3 mL, 2.5 mg/3 mL (0.085%)	Nebulizer	. . .
Aerosol inhaler: 90 μg base/actuation	Metered-dose inhaler with spacer or holding chamber	. . .
Arformoterol 15 μg/2 mL	Nebulizer	Standard jet nebulizer
Epinephrine 1%	Nebulizer	Dilute if using jet nebulizer
Formoterol		
12 μg/capsule	Aerolizer inhaler	Inhale as dry powder; do not use spacer with aerolizer inhaler
20 μg/2 mL	Nebulizer	Inhalation solution for nebulization; administer solution immediately after removal from foil pouch
Levalbuterol		
Aerosol inhaler: 45 μg/actuation	Metered-dose inhaler with spacer or holding chamber	. . .
Nebulizer solution: 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL	Nebulizer	. . .
Metaproterenol		
Aerosol inhaler: 0.65 mg/actuation	Metered-dose inhaler with spacer or holding chamber	. . .
Nebulizer solution: 4 mg/mL (0.4%), 6 mg/mL (0.6%)	Nebulizer	Add 2.5–3 mL of 0.9% sodium chloride injection to 0.2–0.3 mL of drug for nebulization
Budesonide		
Nebulizer solution: 0.25 mg/2 mL, 0.5 mg/2 mL, 1 mg/2 mL	Nebulizer	. . .
Powder inhaler: 90 μg/actuation, 180 μg/actuation	Dry powder inhalation	Do not use spacer for powder inhaler
Cromolyn sodium		
Aerosol inhaler: 800 μg/actuation	Metered-dose inhaler with spacer or holding chamber	. . .
Nebulizer solution: 20 mg/2 mL	Nebulizer	. . .
Ipratropium bromide		
Aerosol inhaler: 17 g/actuation	Metered-dose inhaler with spacer or holding chamber	. . .
Nebulizer solution: 2 mL (0.2%)	Nebulizer	. . .
Acetylcysteine 100 mg/mL (10%), 200 mg/mL (20%)	Nebulizer	10% solution may be used undiluted; dilute 20% solution with sodium chloride or sterilized water for inhalation
Colistimethate 150 mg powder for reconstitution to 75 mg/mL with sterile water for injection (2 mL)	Nebulizer	Further dilute 50–75 mg in 3–4 mL 0.9% sodium chloride injection can be nebulized; immediate use after mixing recommended
Tobramycin 60 mg/mL (5 mL)	Nebulizer	The driving gas should be oxygen
Sodium chloride solution 0.9%, 3%, 7%, 12%	Nebulizer	0.9% solution used as diluent in most inhalation solutions
Dornase alfa 2.5 mg/2.5 mL	Nebulizer	. . .

Development of the compatibility guide

A review of the practices at our institution for mixing aerosolized medications revealed several areas of concern. First, no hospital-approved protocol existed for preparing these admixtures. Second, the document used by our respiratory therapists consisted of a single page listing commonly aerosolized drugs with only "yes/no" information on admixtures and no references establishing the validity of the information. Third, respiratory therapists were often directed to mix aerosolized drugs with no knowledge of the admixture's stability, safety, or efficacy. Fourth, there appeared to be a general lack of knowledge among medical personnel (including pharmacists) about the stability, safety, and efficacy of these admixtures. Finally, references for the compatibility of respiratory admixtures were not readily available to respiratory therapists, nurses, physicians, or pharmacists.

Kamin et al.[3] evaluated the compatibility of common inhalation solutions and summarized their findings in a concise table. Using their table as a template, we prepared a more thorough mixing and compatibility guide in the form of an easy-to-use reference chart (Figure 1)[3,7-14] that includes additional agents and compatibility references and compatibility information for pharmacists, nurses, physicians, and respiratory therapists.[3,4,7-19] Inhaler device recommendations for aerosolized medications are provided in Table 1.[20-23]

Information concerning the stability and compatibility of respiratory admixtures is difficult to locate. The two most extensive resources are often not available to clinicians, nurses, pharmacists, and respiratory therapists and are not comprehensive. Respiratory therapists often prepare respiratory admixtures without proper understanding of what can be mixed safely. In an effort to correct our own knowledge deficiencies, we developed an easy-to-use compatibility chart to guide pharmacists, nurses, clinicians, and respiratory therapists in the mixing and administration of respiratory admixtures. Users of the information in the compatibility chart should recognize the potential limitations of the compatibility determination.

Conclusion

A compatibility guide for aerosolized medications was developed for use by staff who administer these agents.

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