



Pharmacology Update

Janice L. Hinkle, Section Editor

Intrapulmonary Administration of Medications

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The primary objective of any pharmaceutical preparation is to provide the desired drug concentration to the proper site in the body to promptly achieve the therapeutic effect (Hilleman & Banakar, 1992). One of the oldest strategies for drug delivery is inhalation. In the past, inhaled medications have been used for reactive airway disease, chronic obstructive pulmonary disease, or allergic rhinitis. However, aerosolized medications have been increasingly studied for other indications, such as cystic fibrosis, pulmonary hypertension, and diabetes. Intrapulmonary administration of medication provides an alternative route for local administration of agents that are potentially toxic when given systemically or agents that require parenteral administration. This type of therapy may be a feasible alternative for individuals who do not tolerate systemic administration of potentially toxic agents, or who are not able to administer parenteral products by themselves, and may possibly obviate the need for

chronic parenteral therapy for some medications. This unique method of drug delivery has been heretofore used primarily in patients with chronic lung conditions such as cystic fibrosis or in immunocompromised individuals requiring potentially toxic therapies. However, as the experience and success with aerosolizing medications increase, a wider range of patients are likely to benefit. The aim of this review is to highlight some of the information available for using medications once only administered parenterally that are now being given by inhalation therapy.

Aerosolized medications may be delivered to the lower airway either through the nasal cavity or the oropharynx; however, the oropharynx route is preferable for several reasons. First, the alveolar region of the lung provides a larger surface area for drug absorption (approximately 75 sq m) compared to intranasal route (1.5 sq m; Laube, 2001). Alveolar walls are thin and well perfused, allowing rapid drug absorption. The large surface area coupled with the high amount of blood flow through the pulmonary tissues maximizes drug absorption. Second, pulmonary mucociliary clearance mechanisms are minimal in the alveolar region of the lungs. Unlike the terminal portions of the lung, however, the mucociliary clearance of the nasal passages are much more effective (Illum, 2003). Thus, intrapulmonary administration is associated with less rapid elimination of medications com-

pared to intranasal, allowing prolonged deposition time and, for some medications, subsequent systemic absorption. For these reasons, intrapulmonary inhalation seems to be emerging as the optimal route for administration of aerosolized solutions.

Characteristics of Ideal Inhalation Agents

To ensure maximum tolerability of nebulized drugs, the preparation should be sterile, isotonic, preservative free, and pH balanced to 6, similar to the airway epithelium to avoid bronchial irritation (Kuhn, 2002). Many medications currently used for inhalation therapy are solutions formulated for intravenous administration, which may decrease pulmonary tolerability significantly. Some formulations contain preservatives, such as bisulfites or ethylene diaminetetraacetic acid, which may induce coughing, bronchoconstriction, or airway irritation. For example, the intravenous formulation of gentamicin contains phenol. Inhalation and dermal exposure to phenol is irritating to the skin, eyes, and mucous membranes (ATSDR, 1989). This substance also has a very unpleasant taste. In addition, the pH of parenteral gentamicin is approximately 4, further contributing to the likelihood of bronchial irritation (Cole, 2001). As with any medication, individuals receiving intravenous solutions via nebulization should be monitored closely for adverse effects.

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Factors Influencing Aerosol Deposition

In addition to the pharmaceutical preparation, several other factors affect the deposition of inhaled solutions. The lung has a well-defined branching architecture where progressive narrowing of its airways terminates in the alveoli. Therefore, particle size is a critical property governing the extent of deposition of inhaled particles in the lung (Kuhn, 2002; Shek, Suntres, & Brooks, 1994). Large particles (>5 microns) tend to deposit in the upper airways, while smaller particles reach the lower airways, deep into the lung. Submicron particles (<1 micron) have the greatest deposition in the alveoli, allowing the highest systemic absorption (Cole, 2001). Drug retention in the lung is not only dependent upon efficient delivery, but also upon the rate of drug clearance. Medications with small molecular weights typically have relatively short half-lives in the lung, as they tend to be more able to diffuse out of the pulmonary tissue. Liposome encapsulation of medications offers the advantage of preventing premature drug release and increasing drug residence time in the lung, while possibly increasing the tolerability of the inhaled solution (Shek et al.). The pulmonary epithelium acts as a barrier to hydrophilic, ionized medications such as aminoglycosides, limiting systemic absorption (Geller, Rosenfeld, Waltz, & Wilmott, 2003). Other physiochemical characteristics of the drug that may also influence drug deposition into the lung and systemic absorption include protein binding and viscosity (Sermet-Gaudelus et al., 2002).

Mechanically ventilated patients may also benefit from direct delivery of medication into the airways (MacIntyre, 2002). To maximize the deposition of medications in the lower airways of intubated patients, several techniques can be applied including removing secretions from

the endotracheal tube, decreasing inspiratory flow to ≤ 60 L/min, and maintaining tidal volume ≥ 500 ml (Duarte, Heming & Bidani, 2000). Prior to nebulizing a medication in any patient, it is necessary to effectively drain secretions with the help of a mucolytic agent, percussion and postural drainage, or bronchodilation with a beta-2 agonist (Diot et al., 2001). A volume of 4 ml of isotonic saline solution appears optimal for nebulization. Concurrent nebulization of multiple agents should be avoided (Sermet-Gaudelus et al., 2002).

Nebulizing Devices

The device used for inhalation therapy has a large impact on optimal drug delivery. Different devices are available for inhalation therapy including metered-dose inhalers (MDI), dry-powder inhalers, jet nebulizers, and ultrasonic nebulizers. Nebulizers are commonly used in patients with severe airway obstruction and for those agents that are unavailable as MDI or dry powder for inhalation (Le Brun, De Boer, Heijerman, & Frijlink, 2000). Compared to jet nebulizers, ultrasonic nebulizers produce more consistent and efficient aerosols. However, they have a number of limitations such as cost of the device, high maintenance needs, and possible denaturation of active molecules during aerosolization. Thus, ultrasonic nebulizers should not be used for protein drug delivery unless also equipped with a cooling system. Regardless of the nebulizer used, only 8%–12% of the product contained in the canister is actually deposited in the lung (Sermet-Gaudelus et al., 2002). Possible explanations for this poor efficiency are nebulization of the solvent rather than active medication, solution deposition on the canister walls, condensation of the aerosol on the oral mucosa and being swallowed, transmucosal absorption,

and exhalation (Diot et al., 2001; Kuhn, 2002; Sermet-Gaudelus et al., 2002). Powders tend to be better distributed, with 20%–30% of the dose reaching the lower airways (Le Brun et al., 2000; MacIntyre, 2002). The combination of a well-distributed medication, a tolerable pharmaceutical preparation, and an appropriate delivery device is necessary to maximize the delivery of intrapulmonary medications.

The following are examples of aerosolized medications that have been studied and appear to be clinically useful. It is likely that the use of inhalation therapy will become more widespread in the future as the body of clinical evidence supporting the use of nebulized medications for different diseases increases.

Antimicrobials

Amphotericin B deoxycholate is an antifungal agent with a broad spectrum of activity, including deadly filamentous fungi such as *Aspergillus* and *Mucor* (Pfaller, Messer, Hollis, & Jones, 2002). Like colistimethate, amphotericin is associated with severe systemic adverse effects, including nephrotoxicity and hepatotoxicity. While the use of inhaled amphotericin circumvents the systemic toxicities, there are adverse effects when it is administered as an aerosol. Due to its high lipophilicity, amphotericin B is prepared as a colloidal dispersion with deoxycholic acid. In vitro data have shown that nebulized deoxycholic acid may impair surfactant activity (Griese, Schams, & Lohmeier, 1998). A well-functioning surfactant prevents end expiratory collapse of the airspaces, inhibits formation of alveolar edema, and reduces the work of breathing. Therefore, intrapulmonary administration of the deoxycholate formulation may be detrimental to overall lung function. However, the deoxycholate formulation has been used clinically with some success as prophylaxis for

pulmonary aspergillosis (Marra et al., 2002). The typical dose of inhaled amphotericin is 5–30 mg/day, though doses as high as 50 mg/day have also been used. Sterile water for injection should be used as a diluent rather than sodium chloride, as amphotericin is not compatible with ionic solutions such as sodium chloride (Trissel, 2003).

Newer amphotericin preparations have been formulated combining amphotericin with lipid structures for intravenous administration. Amphotericin B encapsulated in a liposome (Ambisome) or complexed with a lipid molecule (Abelcet) may be more tolerable than amphotericin deoxycholate when given intravenously (Dupont, 2002). It also appears that these preparations could possibly be more tolerable than the deoxycholate formulation when inhaled. Liposomal amphotericin has been shown to have no gross effect on the lipid structural organization of the lung, as it has a relatively high surface tension of its own and may represent a more tolerable option (Palmer et al., 2001; Shek et al., 1994). More clinical data are needed before inhaled amphotericin (regardless of the formulation) can be promoted for routine use in prophylaxis or treatment.

Other antimicrobials such as tobramycin and colistimethate (Colistin) have been successfully aerosolized in patients with chronic lung infections, as treatment and prophylaxis (Geller, Pitlick, Nardella, Tracewell, & Ramsey, 2002). Much like amphotericin, these antibiotics are often associated with toxicity when administered intravenously. However, intrapulmonary administration of these agents results in a high concentration in the airways compared to the serum with virtually no systemic absorption and minimal adverse effects (Eisenberg, Pepe, & Williams-Warren, 1997; Geller et al., 2002, 2003). These beneficial characteristics may help renew interest in using potent, but potentially toxic, antimicrobials for local treatment of lung infections.

New Therapeutic Aerosols

More recently, there has been renewed interest in using heparin and insulin via inhalation therapy for the purpose of achieving better systemic absorption (Fiel, 2001; McCann, 2002). Inhalation therapy may offer a more convenient, portable dosage form than injection and offer patients lifestyle options not previously available.

Prostacyclin

Pulmonary hypertension is a life-threatening progressive disease that usually affects the arterial side of pulmonary circulation and often progresses to right heart failure (Peacock, 1999). Most individuals with pulmonary hypertension require vasodilator therapy to lower the pulmonary blood pressures. Although some patients may respond to oral calcium channel blockers, such as nifedipine and diltiazem, for relief of symptoms (Gaine, 2000), those with more severe disease may need a continuous intravenous infusion of a vasodilatory agent such as epoprostenol (Flolan). However, epoprostenol lacks pulmonary selectivity and often causes systemic side effects such as hypotension, nausea, vomiting, jaw pain, and headache. To overcome some of the hazards inherent in systemic vasodilator therapy, aerosolization of prostacyclin analogues, epoprostenol and iloprost, have been shown to be effective for pulmonary hypertension (Olschewski et al., 1996). However, both products have disadvantages. Inhaled epoprostenol has a very limited biological half life of only 2–3 minutes and requires continuous nebulization for optimal effect. In contrast, iloprost has longer half-life and is administered as 100–150 mcg in six inhalations via ultrasonic nebulizer every 2–3 hours while the patient is awake (Gessler, Schmehl, Olschewski, Griminger, & Seeger, 2002). While neither epoprostenol nor iloprost requires prolonged intravenous access, such frequent treatments can still be quite inconvenient for many individuals.

Insulin

Recent studies in human volunteers have shown that aerosolized insulin decreases serum glucose levels similar to those achieved with subcutaneous (SC) insulin during the fasting state. Aerosolized insulin appears to be well tolerated when administered over short periods of time, without any evidence of irritation, hypoglycemia, or reduction in pulmonary function (Laube, 2001). The time to peak insulin serum concentration after intrapulmonary inhalation appears to vary among different patients, insulin products, and disease states. At present, delivery device limitations result in less efficient administration of insulin aerosol compared to SC dosing, so larger doses are usually required. The average bioavailability of the inhaled dose of aerosolized insulin is approximately 20% of a SC injection (Laube, Benedict, & Doba, 1998). The use of inhaled insulin may ultimately be an alternative to frequent subcutaneous injections for diabetic patients.

Heparin

Intrapulmonary heparin was first used in 1970s (Molino & Bellvardo, 1973). Electron microscopy and radiolabeling have revealed that nebulized heparin undergoes immediate uptake by alveolar macrophages, capillaries, and the endothelium of large blood vessels, allowing quick absorption (Mahadoo, Heibert, Wright, & Jaques, 1981). Nebulized calcium heparin has been used with success in treating outpatients with thromboembolic diseases utilizing a weekly treatment regimen (Bick & Ross, 1985). Since heparin also has anti-inflammatory properties in addition to its anticoagulant properties, inhaled heparin for bronchial asthma has also been investigated (Bendstrup, Newhouse, Pedersen, & Jensen, 1999). Calcium heparin tends to be used for inhalation instead of the more familiar heparin salt (heparin sodium) because it contains no additives, is available at a high concentration,

and has less potential for allergic or anaphylactic reactions. The typical dose is 10,000 units of calcium heparin diluted in 5 ml of normal saline per week, although up to 20,000 units per week has been safely administered. Heparin aerosol appears to be well delivered via the DeVilbiss Pulmo-Sonic nebulizer (Bick & Ross, 1985). At this time, there is not enough supportive literature available to advocate the routine use of inhaled heparin for any indication, but like insulin, the availability of a non-parenteral route of administration may prove to be convenient for many patients.

Summary

An increasing number of medications are being administered by inhalation. However, proper dosing, frequency, formulation, and the optimal delivery device remain to be determined for many of these agents. Inhalation therapy has many advantages compared with other routes of administration including achieving a high drug concentration in the lung, lack of systemic adverse effects, ease of administration, and patient convenience. A broad range of patients may benefit from this type of drug delivery. Practitioners must keep abreast of emerging drug administration strategies and new formulations in order to continually improve care for their patients.

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