

## Aerosols for Systemic Treatment

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**Abstract.** The development of a new group of drugs (polypeptides) have recently increased the interest of alternative administration to the enteral route because of its proteolytic activity and the catabolism of the "first-pass effect." Aside from the "needle," the administration in the respiratory tract via aerosol is the method with the best efficiency. But several problems prohibited its spreading: (1) the accuracy and the reproducibility of the inhaled dose (range ca. 1:4); (2) the small amount of inhaled drug in relation to the dose in the aerosol delivery system (range ca. 1%–10%); (3) the fear of allergic reactions of the respiratory system; (4) the variability of the drug transport into the systemic circulation. New approaches and data raise hopes in reducing the problems: (1) aerosol delivery systems with defined particle spectrum and storage systems; slow vital capacity inhaling maneuver; (2) delivery systems that nebulizes nearly the total amount of drug; (3) all studies with the inhalation application of insulin, heparin, ergotamin, ribavirin, aminoglycosides, and "cigarette smoke" do not reveal any relevant allergic reaction; (4) many studies were performed in the last 10 years on the influence of substances and especially of diseases on the transport of molecules through the respiratory tract. Only a few of them are relevant (exogen allergic alveolitis, active sarcoidosis, active smoking). Aerosols for systemic drug treatment seems to be a gained alternative to the "syringe."

**Key words:** Aerosol therapy—Systemic treatment—Topical treatment—Insulin—Heparin.

### Aerosols for Systemic Treatment

Aerosol therapy is very common in obstructive bronchial diseases. There are some other diseases in which aerosol administration of drugs may be of a

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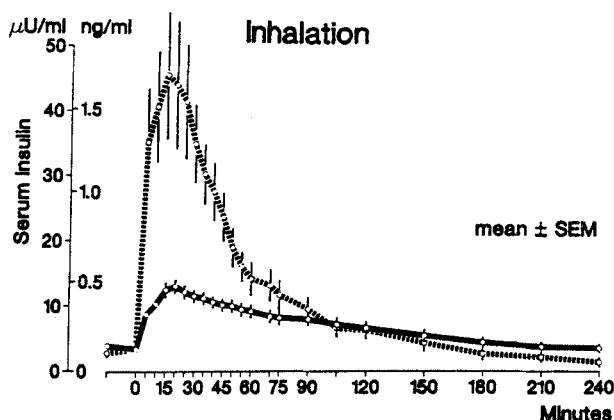


Fig. 1. Time course of serum insulin.

certain benefit. These indications can be divided into topical treatment of the respiratory tract and treatment of systemic diseases. The topical treatment of the lung as discussed in the literature is summarized in Table 1. With the exception of the administration of antibiotics, antiviral agents, and vaccines, the other indications have not been widely used and are therefore uncertain. Some of them are only anecdotal.

A similar situation exists with respect to the administration of aerosols for systemic purposes is shown in Table 2. Only the treatment of headache with ergotamine [14] as a metered-dose inhaler is established (Table 3). Some work has been done on the aerosol administration of insulin [28, 42, 50]. All these studies have shown rapid transport of insulin into the blood with a half-life of approximately 15–25 min. However, the total amount of insulin deposited in the respiratory tract was unknown in all these studies. The poor reproducibility of the inhaled dose was always the reason for terminating these experiments.

We performed a study with inhalation of human insulin in 12 volunteers (five smokers and seven nonsmokers) using a special aerosol administration device (AMMD  $< 2 \mu\text{m}$ ), which allows the estimation of the intrabronchially deposited dose [28, 42]. The inhalation device was calibrated with  $^{99\text{m}}\text{Tc}$ -DTPA-aerosol in each volunteer. The time course of the serum insulin (the endogenous insulin is subtracted) and the plasma glucose is given in Figs. 1 and 2. The dose of insulin transported into the blood was approximately 30% in the non-smoking group and approximately 65% in the smoking group. It can be assumed that the missing proportion is either stored in the bronchial cells or disturbed by the proteolytic enzymes in the bronchial tree.

Interestingly the serum insulin peaks occurred at a similar time in both groups (Fig. 1). This leads to the assumption that the transport across the bronchial mucosa is an active mechanism, not simply diffusion. Bhalla and Crocker have shown this mechanism for albumin and peroxidase [2].

Completely different are the problems encountered with the inhalation of heparin. The inhaled heparin seems to be stored and slowly released from the

**Table 1.** Topical Treatment of the Lung Via Aerosol (except obstructive diseases)

Antibiotics and antiviral agents	Aminoglycoside	Cystic fibrosis [6, 20]
	Carbenicillin	Bronchiectasis [25, 49]
	Pentamidine	AIDS [34]
	Ribavirin	RS-virus infections [1, 12, 15, 47] Exacerbation of chronic bronchitis(?) [15, 49] Pneumonia [25]
Immunosuppressive agents	Steroids	Lung fibrosis [17]
	Interferon(?)	Bronchial-amyloidosis(?)
	Antioxidant	
Antielastase	New drugs	Emphysema(?) [45]
Vaccines	Bacterial	Chronic bronchitis
	Viral	Infectious diseases
Surfactant	Different sources	IRDS + ARDS [24, 51]
		Asthma(?)
Protease	Trypsin	Alveolar proteinosis [23]
Antitumor agents	Interferon	Prevention of bronchial-cancer(?)
	Antioxidant (vitamin A + E)	
Anticold agent	Hot mist (>42°C)	Cold [46, 48, 49]

**Table 2.** Systemic treatment via aerosol

Ergotamine		Migraine [14] Histamine headache [14] Vascular headache [14]
Insulin		Diabetes [28, 42, 50]
Heparin		Anticoagulation [3, 31, 35] (prevention of DVT, LE, myocardial infarction)
		Prevention of [9, 22, 43] atherosclerosis
Polypeptides	Calcitonin	Osteoporosis
	Releasing hormone	Different diseases
	New drugs	
Prostaglandins	Prostacyclin	Primary pulmonary hypertension
Nicotine		Smoking cessation [5, 39, 40]
Miscellaneous	Calcium antagonists	CHD(?)

**Table 3.** Efficacy of ergotamine given by various routes

Drug	Results (%)			Time of Onset (min)
	Good	Fair	Poor	
Ergotamine inhalant	57	15	28	15-30
Ergotamine-caffeine suppositories	73	17	10	90-120
Ergotamine tablets sublingual	45	24	31	45-60

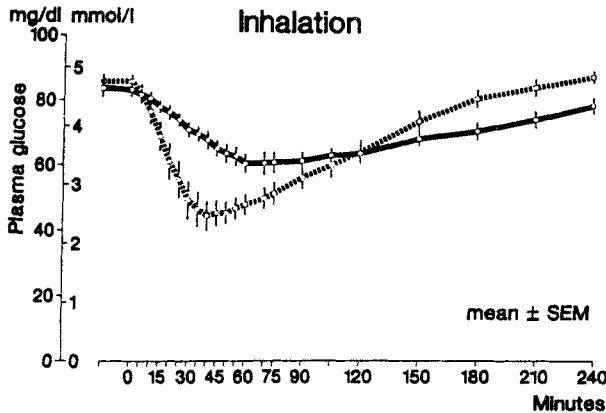


Fig. 2. Time course of plasma glucose.

macrophages or in the bronchial cells [3, 31], because the antithrombotic effect of heparin was seen over more than 24 h. No data are available about the characteristics of low-molecular-weight heparin. Heparin generally seems to be a promising substance, because it has an antithrombotic and preventive effect not only on the postmyocardial survival rate [35], but also on atherosclerosis [9, 23]. As yet, heparin is the only drug known to be able to reverse sclerosis [43].

Less information exists about the intrabronchial administration of polypeptides and prostaglandins by aerosol. Nasal administration is most common. But in future polypeptide drugs will be of greater interest owing to their short half-life and primary influence on the biologic cybernetic system.

To ameliorate the side effects associated with cessation of smoking, a nicotine aerosol is sometimes used [5, 39]. The aerosol administration of nicotine is superior to oral or transcutaneous administration, because it imitates administration via cigarette smoke. The pulsatile pharmacokinetics of nicotine are primarily responsible for abuse [40].

The two main factors preventing the spread of this route of administration are the unsteadiness in dosimetry and the interdisciplinarity of this problem. The influences on the action of the drug from its generation to transport into the blood are very complex and can be divided into six steps (Fig. 3):

The *drug* itself must be acceptable for inhalation (pK, solubility, taste [26, 40]). In addition, hygroscopy influences its growth in the water-saturated part of the bronchial tree [10, 29, 30]. For the development of a convenient administration system it would be better if the drug could be micronized [7].

The *aerosol generator* (or delivery system if the drug is micronized) must produce particles that are small enough to achieve an adequate intrabronchial deposition [4, 8, 18, 27, 32, 44, 46]. On the other hand, the aerosols must be big enough to transport a sufficient amount of substance into the lung (volume  $\sim$  diameter<sup>3</sup>). Furthermore, the particle spectrum from the nebulizer should not be influenced by the inspiratory flow (closed system) [13, 26]. To keep the

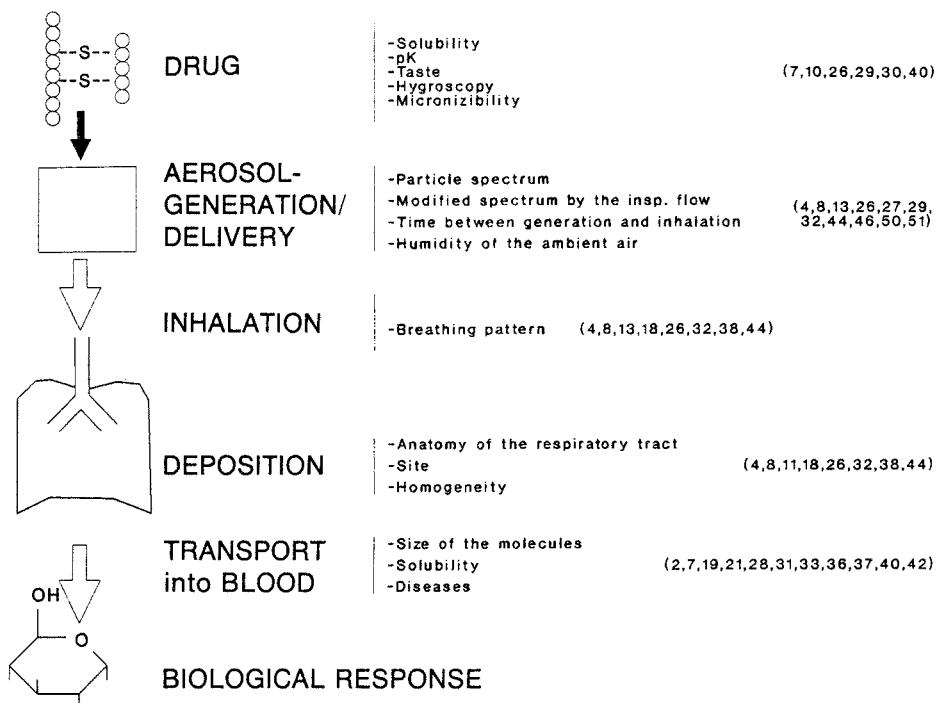


Fig. 3. Flow chart representing the influences on the action of the drug from its generation to transport into the blood and final biological response.

alteration of the particles constant, the time between generation and inhalation should not differ remarkably. The humidity of the ambient air is rarely noticed to determine the additional weight loss of the nebulizer solution by evaporation [13, 32]. This itself influences the concentration of the drug in the aerosol generator during nebulization [13, 26, 51]. Ultrasonic nebulizers should be used with caution because they can alter complex organic molecules [50, 51].

The *inhalation maneuver* has a noticeable influence on the amount of aerosol deposited in the bronchial tree [4, 8, 13, 18, 26, 32, 38, 44]. The most reliable maneuver is the slow deep breath (similar to a slow vital capacity maneuver) with a breath-holding time of  $>5$  s.

The above-mentioned influences on the aerosol *deposition* in the respiratory tract are modified by anatomy, especially from the area glottica [4, 8, 11, 18, 26, 38, 41]. The site of deposition varies with the anatomy and the degree of bronchial obstruction. This also influences the exhaled dose and the inhomogeneity of the deposition [8, 26, 41].

The *transport* of the drug into the blood must be measured separately for each chosen drug. It depends on the size of the molecules [2, 19, 28, 36, 37, 40, 42], the water/lipid solubility and pK [7, 19, 31, 36, 40] and is increased by

cigarette smoking as well as some other diseases (e.g. active sarcoidosis, exogenous allergic alveolitis, ARDS, pneumocystis carinii infection [19, 21, 28, 33, 36, 41]).

In summary, the administration of drugs for systemic purposes via aerosol inhalation should be more appreciated. Improved aerosol administration devices now available that allow a more precise aerosol deposition in the bronchial tree raise hope for advances in this form of drug administration.

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