
Inhaled (Non-bronchodilator/ non-steroid)
pharmacologic therapeutics-rationale,
approaches and limitations

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Introduction

- The use of aerosolized medications for treatment of the respiratory diseases has a long history in medical therapy
- 17th-century Ayurvedic literature- smoking of Datura group of herbs for dyspnea
- Inhaled Datura for asthma was recorded in 1802 in Britain
- Asthma cigarettes were widely used in the 19th century as “fuming asthma remedies”

Advantages of the Inhalation Route

- Aerosol doses are generally smaller than systemic dose
- Onset of effect is faster with inhalation than with oral administration
- The drug is delivered directly to the target organ with minimized systemic exposure
- Systemic adverse effects are less severe and less frequent
- Inhaled drug therapy is painless and relatively comfortable

Inhaled (Non-bronchodilator/ non-steroid) pharmacologic therapeutics

- Inhaled antibiotics
- Inhaled anti fungal
- Inhaled Antitubercular drugs
- Inhaled insulin
- Inhaled Vaccines
- Inhaled gene therapy

Antimicrobial inhaled therapy

Aerosolized Tobramycin

- 80% of CF patients colonized with *P. aeruginosa*, and 90% of all CF patients die due to progressive pulmonary disease.

(Koch C et al. Lancet 1993; 341:1065–1069)

- Inhalation tobramycin offers high concentrations of antibiotic to the site of infection while minimizing systemic bioavailability

(Touw DJ et al. Eur Respir J 1995; 8:1594–1604)

Antimicrobial inhaled therapy

Aerosolized Tobramycin

Rationale for aerosol Tobramycin

- High concentrations in the lung can be obtained
- Only a small fraction of the inhaled antibiotics is absorbed
- Less disturbance of the host micro-organism

Antimicrobial inhaled therapy

Aerosolized Tobramycin

- Inhaled tobramycin used IV preparations which may cause bronchoconstriction
- High-dose, preservative-free tobramycin (600 mg thrice daily) delivered by an ultrasonic nebulizer improving PFT and decreasing the sputum density of *P aeruginosa*
- Jet nebulizer could achieve high sputum levels of tobramycin in most CF patients with only a 300-mg nominal dose

(Eisenberg J et al. Chest 1997; 111:955–962)

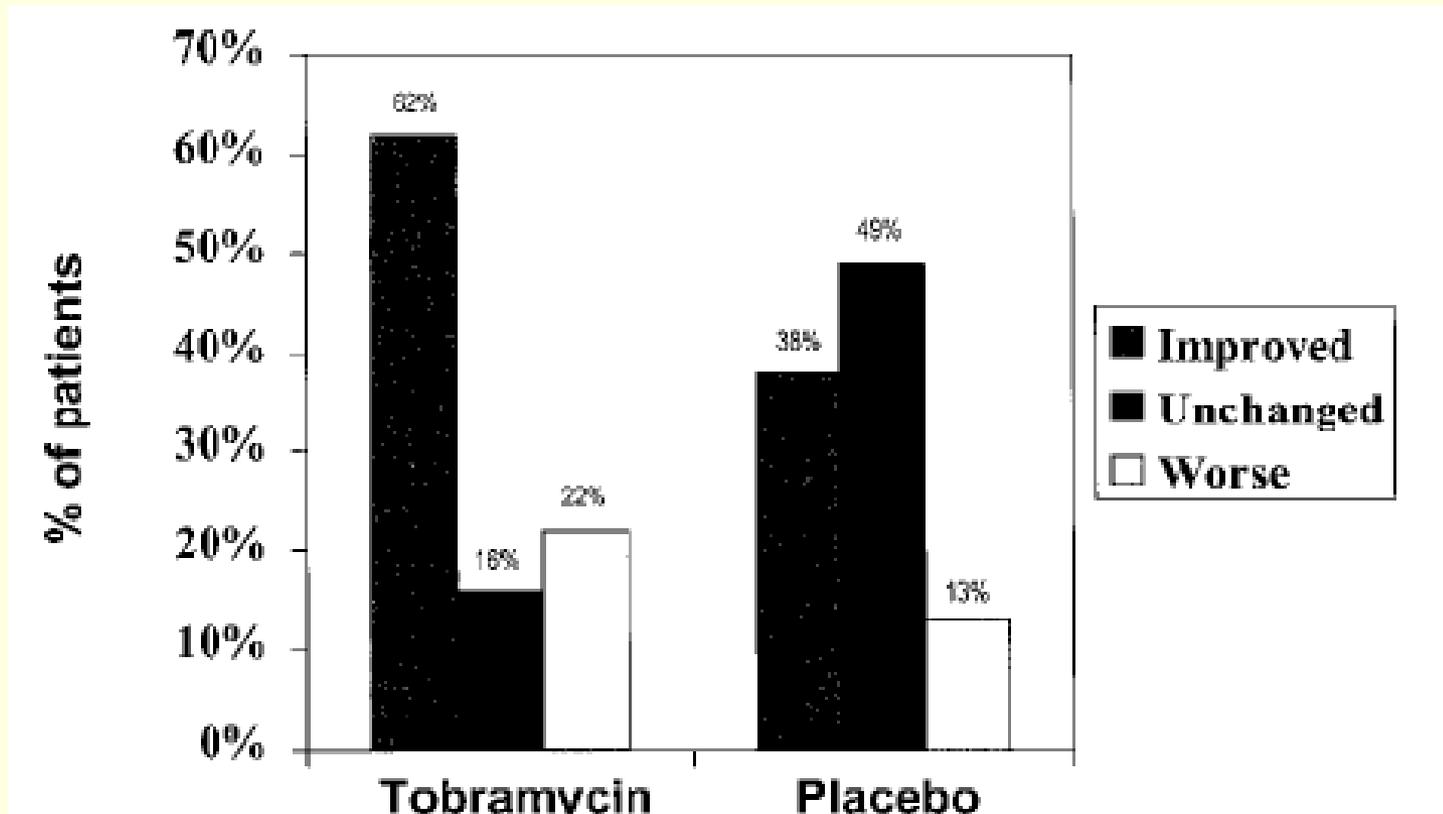
Tobramycin Inhalation

Severe Bronchiectasis

- TSI therapy significantly improve in respiratory symptoms and HRQL in subjects with severe bronchiectasis
- But some subjects did not tolerate TSI therapy.
- Bronchiectasis patients receiving this therapy should be monitored for signs of intolerance.

(Paul Scheinberg et al. CHEST 2005; 127:1420–1426)

Tobramycin Inhalation Severe Bronchiectasis



(Leslie A. Couch et al. *Chest* 2001;120;114-117)

Antimicrobial inhaled therapy

Aerosolized Tobramycin

- Long-term treatment with TSI for upto 2 years resulted in
- Sustained improvement above baseline values in FEV1
 - Fewer hospitalizations
 - Increased weight gain
 - Lesser need for IV anti-pseudomonal therapy

(Bonnie WR et al. NEJM 1999;340:23-30)

Aerosolized Aminoglycoside in VAP

- Aerosolized antibiotics decrease secretion volume and reduce bacterial growth
(Smaldone GC et al. Resp Care 2004;49:635-639)
- Advance in aerosol drug delivery to mechanical ventilated patients will result in greater drug delivery to the lung, and possibly improve efficacy
- Ventilators should nebulize during inhalation with flow rates >6L/min, which improves lung deposition
(Wood GC et al. Pharmacotherapy 2000;20:166-181)

Aerosolized Aminoglycosides in VAP

- Optimal benefit has been shown in nebulizers that are positioned within 30 cm of the ET tube in the inspiratory limb .
- Adjunctive inhaled antibiotic is a potential targeted therapy for VAP in high risk population
- Systemic concentrations of aminoglycosides after aerosol therapy are low, so, there is no adverse effects reported

(Alicia M et al. Surgical infections. 2007;8:3)

Aerosolized Aminoglycoside in VAP

AA along with systemic therapy for VAP is associated with

- Clinical resolution of pneumonia
- Liberation from mechanical ventilation
- Minimal risk of antibiotic resistance

(Alicia M. et al. Surgical infections 2007;8:3)

Inhaled Colistin

- Colistin, a polymyxin, has been shown *in vitro* to be active against *P. aeruginosa*
- In 1963, Pino et al. first described the use of aerosolized colistin for pulmonary infection
- Use parenterally has been limited by systemic toxicity

Inhaled colistin

- Inhaled colistin maintenance of pulmonary function and in ↓ the frequency and number of pseudomonas
- Inhaled colistin may be considered as adjunctive to IV treatment in patients with VAP due to MDR-GNB susceptible to colistin in critically ill patients
(Michalopoulos A Critical care 2005;R53-R59)
- Although colistin is safe and effective, the best route of administration remains unclear

Antitubercular inhaled therapy

- Boiling tar vapours, became a popular antitubercular medication in the middle of the 20th century
- ATD delivery via the pulmonary route would help in
 - (i) direct drug delivery to the diseased organ
 - (ii) targeting to alveolar macrophages
 - (iii) reduced systemic toxicity of the drugs
 - (iv) improved patient compliance

Antitubercular inhaled therapy

- Liposome-encapsulated drugs are especially effective against intracellular pathogens
- Liposomal formulation helps in the persistence of rifampicin in the lung tissue
- There is equivalent therapeutic efficacy of twice weekly nebulized liposomal rifampicin and daily conventional rifampicin in a murine TB model.

(Rajesh Pandey et al. Journal of Antimicrobial Chemotherapy (2005) 55, 430–435)

Pulmonary delivery of nanoparticle-encapsulated ATDs

- Nanoparticles(10-1000nm) to achieve a high drug loading, and elicit a better therapeutic response
(Pandey R et al. 2004 Current Drug Delivery 1, 195–201)
- Inhalable nanoparticles stand better chances of mucosal adherence, particle(s) delivery and hence net drug delivery to the lungs
(Jacobs C et al.2002,Pharmaceutical Research 19, 189–94)

Pulmonary delivery of nanoparticle-encapsulated ATDs

- A single nebulization to guinea pigs was able to maintain a therapeutic drug concentration in the plasma for 6–8 days and in the lungs for 9–11 days
- In *M. tuberculosis* infected guinea pigs, five nebulized doses of the formulation spaced 10 days apart, resulted in undetectable cfu in the lungs

(Pandey R et al. 2003 Journal of Antimicrobial Chemotherapy 52, 981)

- Capreomycin in DPI can be efficiently delivered to the lungs of guinea pigs, high local drug exposure but significantly reduced systemic exposure.

(Fiegel J et al. Pharm Res. 2007 Jul 27)

Inhaled $\text{INF}\gamma$ in MAI

- Human alveolar macrophages can be selectively activated by the use of IIFN γ
- IFN γ 500 μg 3 d per week for 5 wk , numbers of MAI \downarrow in the sputum and the number of colonies \downarrow significantly
- IIFN γ can be considered as an adjuvant to conventional drug therapy, with a good tolerance, in cases of lung disease caused by resistant MAI

(AJRCCM 1995 ; 152: 3, 1094-1096)

Inhaled Amphotericin B

- March , 2006 FDA has approved ABI in the prevention of pulmonary fungal infections (Af)
- Patients at risk of developing the infection may potentially reduce the incidence of infections, morbidity and mortality and significant treatment costs
- ABI is the first anti-fungal therapy that is inhaled to be under development for immuno-suppressed patients.

(Roth C et al. Infection. 1996 Sep-Oct;24(5):354-60)

Inhaled pentamidine

- Inhaled pentamidine therapy is indicated for the primary and secondary prophylaxis of PCP in patients with HIV infection
- A dose of 300 mg of aerosolized pentamidine given every four weeks was well tolerated and 60 to 70 percent effective in preventing a first episode of PCP in patients with HIV infection.
(NEJM; 324:1079-1083 1991 Number 16)
- Failure of inhaled pentamidine prophylaxis is seen almost exclusively among patients with CD4 lymphocyte counts below 60/mm³.

(Chest 1993;103;342-344)

Inhaled insulin therapy

- Human insulin in dry-powder form as a rapid acting inhaled therapy approved by FDA January 2006
- Available as pre-packed individual blisters in 1 mg dose which deliver 3 u of insulin, and 3 mg dose which delivers about 9 u of insulin.

Inhaled insulin therapy

Patients considered not appropriate

- **Smokers (current and recent):**
(Becker RH et al. Diabetes Care 2006;29:277-82)
- **Patients with (COPD) or asthma**
- **Pregnancy and patients under 18 years**

Inhaled insulin therapy

- Bioavailability of inhaled insulin is 10%. Large part of inhaled insulin remains unabsorbed, in upper respiratory tract or inhalation device, part of it is possibly exhaled.
- Lung function: more reduction in FEV 1 occurs with inhaled insulin
(Hollander PA et al. Diabetes Care 2004;27:2356-62)
- The significance of insulin-binding antibodies (IgG) is unclear

Inhaled insulin therapy

- Patients treated with IDPI reported significantly greater improvements compared with SC insulin or oral agent therapy

(Daily G, Clin Ther. 2007;29:1271-83)

- IDPI consistently improved glycemic control, whether used in combination with NPH in patients with type 1 or type 2 DM or to supplement or replace oral agent therapy in patients with type 2 DM.
- IDPI is associated with an acceptable tolerability profile, with a risk of hypoglycemia similar to that of SC insulin

(ADA 2006, 66th Annual Scientific session)

Inhaled iloprost

- Inhaled iloprost is a safe, effective, and well-tolerated treatment for severe PAH
- It is currently approved in Europe for IPAH in patients in NYHA functional class III
- Important drawback of inhaled iloprost is related to the relatively short duration of action, requiring the use of six to nine inhalations a day
- In patients with pre-existing PHT undergoing mitral valve surgery, inhaled iloprost is superior to intravenous nitroglycerine by acting as a selective pulmonary vasodilator

(RexS et al. Acta Anaesthesiol Scand. 2007 Nov 1)

Inhaled iloprost

- In IPAH, acute inhalation of iloprost resulted in a more potent pulmonary vasodilator effect than acute NO inhalation
(Hoepfer MM et al. J Am Coll Cardiol 2000; 35:176–182)
- Inhaled iloprost at a daily dose of 50 to 200 µg in 6 to 12 inhalations a day improved functional class, exercise capacity, and pulmonary hemodynamics
(Olschewski H et al. Ann Intern Med 2000; 132:435–443)
- Iloprost could improve quality of life in patients with hepatopulmonary syndrome waiting for liver transplantation and post surgery until the resolution of the hypoxemia
(Krug S et al. Eur J Gastroenterol Hepatol. 2007 Dec;19(12):1140-3)

Inhaled nitric oxide

- Nitric oxide is a ubiquitous, highly reactive, gaseous, diatomic radical that is important physiologically at very low concentration
- INO therapy leads to an improvement in oxygenation without short-term side effects in premature infants with severe RDS and respiratory failure

(Su PHJ Perinatol. 2008 Feb;28(2):112-6)

- Early routine use of INO in mildly sick preterm infants may decrease serious brain injury and may improve survival without BPD

Inhaled nitric oxide

- INO reducing lung injury by ability to scavenge O₂ free radicals, ↓O₂ toxicity, ↓platelet and leukocyte aggregation
- INO selectively improves blood flow to ventilated alveoli, which produces a reduction in intrapulmonary shunt and improved oxygenation
- Indication:-ARDS,HRF of Newborn, PPH, Bronchospasm, Sickle cell disease, CT surgery, HLT

Inhaled furosemide

- **IF release the bronchodilator prostaglandins from the airway epithelium**
- **IF works by inhibiting both cholinergic and excitatory nonadrenergic, non cholinergic neurotransmission**
- **Bronchoconstriction that follows the inhalation of lysine-aspirin can be blocked by the inhalation of 20 mg of furosemide**

Inhaled furosemide

- IF shown to have an inhibitory effect on the cough response and to prevent bronchoconstriction in patients with asthma
(BiancoS et al.1988 *Lancet* 2:252–255.)
- Vagal afferent fibers may play an important role in modulation of the sensation of dyspnea, it is possible that IF may modify the sensation of dyspnea

(AJRCM., Volume 161, Number 6, June 2000, 1963-1967)

Inhaled Gene Therapy

There are a number of advantages to this

- First, aerosolized gene therapy provides a direct, noninvasive means for targeted delivery to different regions of the lung.
- Second, this route of administration delivers a high dose to the target site.
- Third, aerosolized gene therapy causes fewer adverse effects than intravenous administration.

Inhaled DNA to Cystic Fibrosis

- The most visible gene therapy drug under development is inhaled complementary DNA to treat CF
- The goal of aerosolized gene therapy in treating CF is to reconstitute CFTR function and normal chloride channel function in the lungs

Inhaled DNA to Treat Lung Cancer

- Binding of DNA with cationic polypeptides such as polylysine, polyethyleneimine, protamine, and histones may be useful for gene delivery
- Aerosol delivery of polyethyleneimine DNA complexes results in substantial gene expression in the lungs of mice

(Gautam A et al. Mol Ther 2000;2(1):63–70)

- Aerosol polyethylenimine-p53 therapy and aerosol polyethyleneimine interleukin-12 therapy significantly reduce the number and size of osteosarcoma lung metastases

(Densmore CL et al. Cancer Gene Ther 2001;8(9):1–9)

Aerosolized Vaccination Advantage

- Avoids the need for disposal strategies for the large number of needles that would be used in mass vaccination campaigns in developing countries.
- Second, it prevents the spread of blood-borne diseases such as HIV
- Third, it induces protection by exposing the airway mucosa to virus
- Finally, it may work better with young children, in whom the persistence of maternal antibodies does not appear to interfere with mucosal immunization but does interfere with subcutaneous immunization.

Influenza Vaccine Aerosol

- Live, attenuated influenza vaccine that is a liquid and is administered via nasal spray
- Intranasal administration reduces the incidence of influenza and is well tolerated
(McCarthy MW et al. *Ann Pharmacother* 2004;38(12):2086–2093)
- Spray-dried formulations that contain whole inactivated virus is more effective than parenteral or nasal administration
(Smith DJ et al. *Vaccine* 2003;21(21–22):2805–2812)

Measles Vaccine Aerosol

- Albert Sabin, and their associates proved the feasibility of vaccination with aerosolized measles vaccine
- Measles vaccine administered via aerosol provides a superior boosting response, compared to vaccination by injection in school-age children
(Bull World Health Organ 2002;80(10):806–812)
- WHO decided to aerosolize the liquid formulation that is currently licensed for injection therapy for mass immunization campaigns

Inhaled immunosuppressive

for the prevention of pulmonary graft rejection

- Inhaled corticosteroids have been shown to be effective in preventing obliterative bronchiolitis in patients at risk after heart-lung transplantation
- Inhaled cyclosporin has also been reported to be more effective than oral administration, with substantially lower blood concentrations
- This new approaches to targeting immunosuppressive treatment could have specific advantages in long term therapy of lung and heart-lung transplant recipients

(Akamine S et al.BioDrugs. 2006 Jan;9(1):49-59)

Inhaled UFH

- UFH change the morphology and rheology of sputum in CF patients
- Actin-DNA bundles in CF sputum were disaggregated by UFH
- The mucoactive properties of UFH indicate its potential as a new therapeutic approach in patients with cystic fibrosis.

(Am J Physiol Lung Cell Mol Physiol. 2007 Nov;293(5):L1240-9)

Inhaled UFH

- Current pilot study demonstrated no evidence of improved sputum clearance with 50,000 IU of inhaled heparin given twice daily to adult cystic fibrosis subjects
- Heparin inhalation had no significant effect upon FEV1, symptoms of sputum clearance or sputum inflammatory markers

(Eur Respir J. 2006 Feb ;27 (2):354-358 16452592)