Inhalational Devices for the Outpatients

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Introduction

- Inhalational therapy allows selective treatment of lungs
  - achieving high concentrations in airway
  - minimizing systemic effects
- Inhaled β-2 agonist produce more rapid onset of action as compared to oral
- Some drugs are only active with aerosol delivery
  - Asthma→ cromolyn & ciclesonide
  - CF →- dornase alfa
- Aerosol drug delivery is painless & convenient

Introduction

- Asthma guidelines favor aerosol inhalation over oral / parenteral
- NHLB Institute/WHO/ GOLD recommends bronchodilator as central to symptom management in COPD patients & inhaled therapy is preferred

Am J Respir Crit Care Med 2001; 163:1256–1276

- Disadvantages → specific inhalation techniques necessary for proper use
- Decreased drug delivery if technique is not optimal leading to reduced efficacy

Historical aspect

- Inhaled therapies
  - since ancient times
  - ? origins with smoking of datura preparations in India 4,000 years ago

- 18th & 19th century- earthenware inhalers were used for inhalation of air drawn through infusions of plants and other ingredients

- Atomizers and nebulizers developed in mid-1800s in France
  - an outgrowth of the perfume industry
  - response to fashion of inhaling thermal waters at spas

- 20th century - combustible powders & cigarettes containing stramonium were popular for asthma & other lung complaints

- 1st pMDI was developed by Riker Laboratories in 1956 for epinephrine & isoproterenol

- Remarkable advances in the technology of devices & formulations for inhaled drugs in past 50 years

- Influenced greatly by scientific developments in several areas
  - Theoretical modeling & indirect measures of lung deposition
  - particle sizing techniques
  - in vitro deposition studies, scintigraphic deposition studies
  - pharmacokinetics and pharmacodynamics
  - 1987 Montreal Protocol, which banned chlorofluorocarbon propellants

- Era of rapid technologic progress in inhaled drug delivery & applications of aerosol science & aerosolized route of drugs for
  - systemic therapy
  - gene replacement therapy
  - aerosolized antimicrobial & immunosuppressants

aero’ air

‘sol’ solution

Particles which are sufficiently small so as to remain airborne for a ‘considerable’ period of time

- Pulmonary deposition achieved by 3 key mechanisms
  - inertial impaction
  - Sedimentation
  - diffusion
- Operate in different combinations for different aerosol drugs at different sites in pulmonary tree

- **Inertial impaction** – predominantly in oropharynx & larger airways for aerosols with relatively large particle size (>3µ)

- **Diffusion** - Brownian motion is dominant mechanism for the smaller sized aerosols (<0.5µ)

- **Sedimentation** – (1-3µ) in small airways & are enhanced by breath holding

Factors affecting inhaled drug delivery

- **Physical Characteristics of the Aerosol Particle**
  - Size (mass median aerodynamic diameter)
  - Density
  - Electrical charge
  - Hygroscopy
  - Shape
  - Velocity of the aerosol particles
- **Host Factors**
  - Inspired volume
  - Inspiratory time
  - Inspiratory flow
  - Breath-hold duration
  - Timing of aerosol delivery during inspiration (with MDI)

TYPES OF DEVICES

Drug (solid or liquid)

MDI/DPI

Small volumes
Ready to use

Nebulizers

High fill volume (>1ml)
Preparation required

MDI **DPI**

Stable obstructive disease

Jet nebulizer **Ultrasound nebulizer**

Severe respiratory insufficiency

MDI

- First MDI used in 1955 included
  - 50µL metering device
  - 10mL amber vial
  - plastic mouthpiece with molded nozzle

- Next year surfactant & micronised powder were added to propellant, creating first commercially available formulation

Postgrad Med J 1956; 20: 667-73

- Modern MDI comprises of a pressurised metal canister containing
  - mixture of propellants
  - Surfactants
  - Preservatives
  - Drug

MDI

- Consist of a
  - micronised form of the drug in a propellant under pressure
  - surfactants to prevent clumping of drug crystals
  - Lubricants for the valve mechanism
  - solvents
- Actuation exposes propellant to atmospheric pressure & causes aerosolisation of drug

- As it travels through air → aerosol warms up leading to evaporation of propellant that reduces particle size to desirable range

- Fraction of drug to airways ranges from 5 percent to 15 percent

Respir Care 2005; 50: 367-82

MDI

- pMDIs have traditionally used chlorofluorocarbon gases as propellants
- CFC gases implicated in causing depletion of O_3
- US FDA issued a final mandate in 2005 requiring that CFC inhalers be entirely removed from the market by December 31, 2008
- In India, Drug Regulatory Authorities have given a deadline that by 2010, all MDIs should be replaced with HFAs
- Substitution of HFA for CFC → changes in pharmacokinetic profile of drugs

MDI

	CFC	HFA
Form	suspension	solution
Surfactant	yes	No Alcohol added for dispersion
Particle size		finer & softer
Speed	High	Slower
Oropharyngeal deposition	More	Lesser

50% of the usual dose used in CFC MDIs was required to produce the equivalent clinical effect

RespirMed 1998; 92 (Suppl.): 9-15

MDI - Disadvantages

- Most patients cannot coordinate inhalation with actuation →reduction in amount of drug reaching airway
- Pt may stop inhaling when aerosol cloud hits back of throat → "cold freon effect" - eliminated in CFC-free inhalers
- MDI alone increases oropharyngeal deposition →local side effects especially with steroids
- Delivered dose may vary when MDI is not shaken properly
- Difficult to know when the MDI is empty
- Cumbersome to teach

Table 4 Technical aspects related to MDI use tending to influence drug deposition in the lower airways.

Inhalation technique	Drug dose reaching the lungs
Poor delivery/inhalation timing	As low as 0% of the expected dose
Quick inhalation and 10 s end-inspiratory pause in a patient with very good timing	Approx. 7%[35]
Slow inhalation and 4 s end-inspiratory pause	Approx. 6.5%[35]
Slow inhalation and 10 s end-inspiratory pause	Approx. 14 to 50%[35–37]
Delivered volume 25 µl	Approx. 17%[38]
Delivered volume 50 µl	Approx. 12%[39]
Delivered volume 100 µl	Approx. 9%[40]
Failure to shake the canister	Approx. 50% of the expected dose[41]

Pulmonary Pharmacology & Therapeutics (2001) 14, 351–366

MDI

Some of problems can be eliminated by

- Proper patient education
- Correct inhaler usage technique
- Rinsing the mouth after every use
- Use of a spacer
- Use of breath actuated MDI
- Use of dry powder inhalers (DPIs)

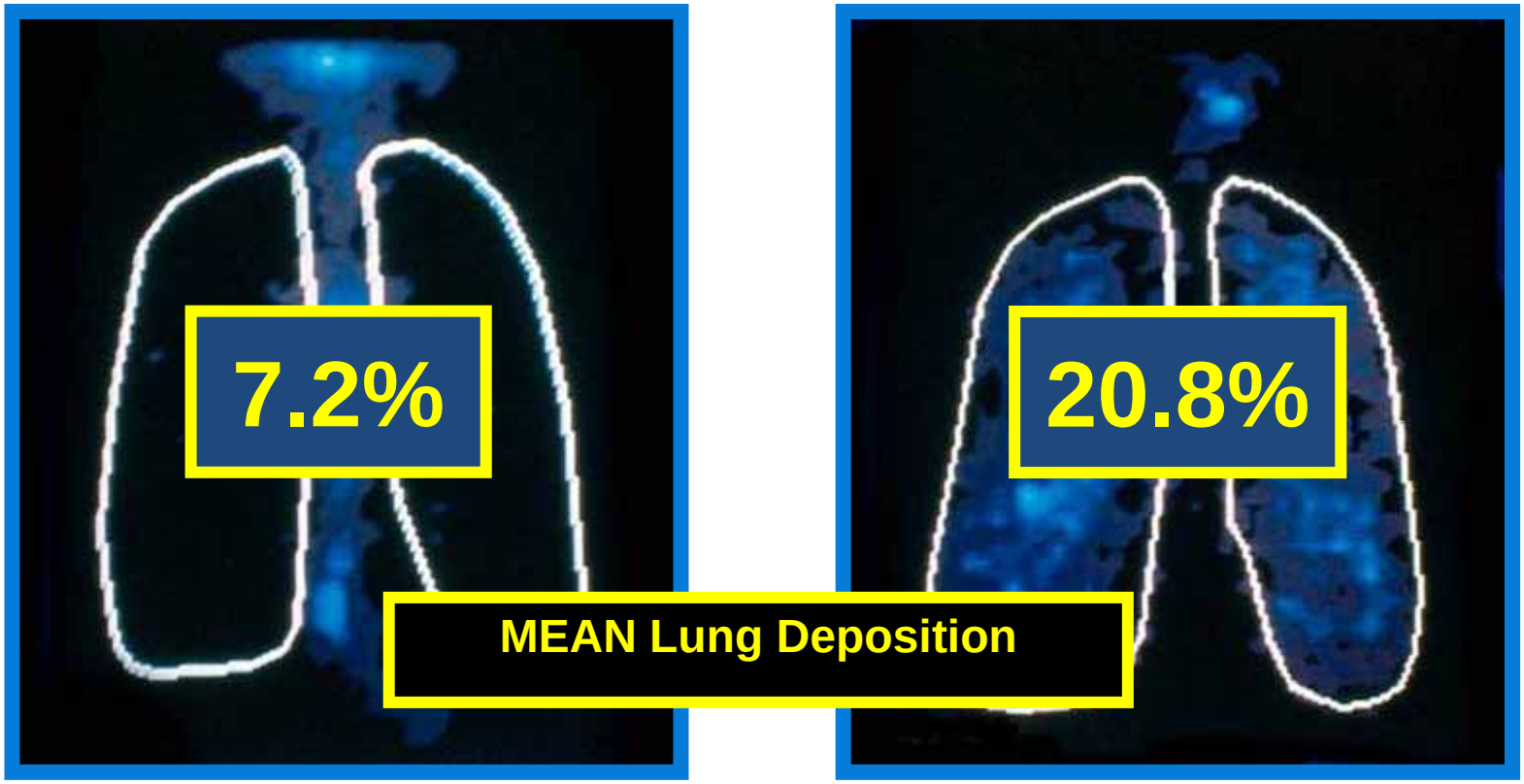
MDI - Autohaler

- 1st breath-actuated or activated pressurized (BAI)
- Overcomes problem of coordination of actuation with inhalation
- It is activated at resting flow rates (as low as 20–36 L/sec.)
- Key features of the Autohaler
  - Patient inhalation triggers the release of the drug
  - No need to coordinate actuation and inhalation
  - Activated at a flow rate of 20–30 L/min
  - Audible soft “click” or a “whoosh” sound to confirm dose dispensation

MDI

- **The Autohaler: Key characteristics**
  - Breath-acutated pMDI: No coordination required
  - Needs just 22-30 L/sec for actuation
  - Simple to learn and use
  - Easy to teach
  - Indicated for adults, the elderly and children
  - Can be used in difficult situations
    - acute wheezy children
    - adults with severe airflow obstruction, etc

Drug Deposition with the Autohaler™ Inhalation Device



Press & Breath inhaler poor coordination

Autohaler™ Inhalation Device same patient

Thorax. 1991; 46(10):712-716

Spacer / valved holding chamber

- Adjunct to overcome problem related to coordination & is useful for old patients & those unable to hold breath

- Advantages include
  - improved coordination with inspiratory flow of patient
  - reduction of overall particle size of inhaled aerosol as larger particles tend to stick to chamber walls/valves
  - reduction in particle velocity → decreased upper airway deposition

- Aerosol must be inhaled immediately after MDI is discharged & only a single actuation for each inhalation

- Instructed to breath in and out for a few breaths before actuating another discharge

Spacer / valved holding chamber

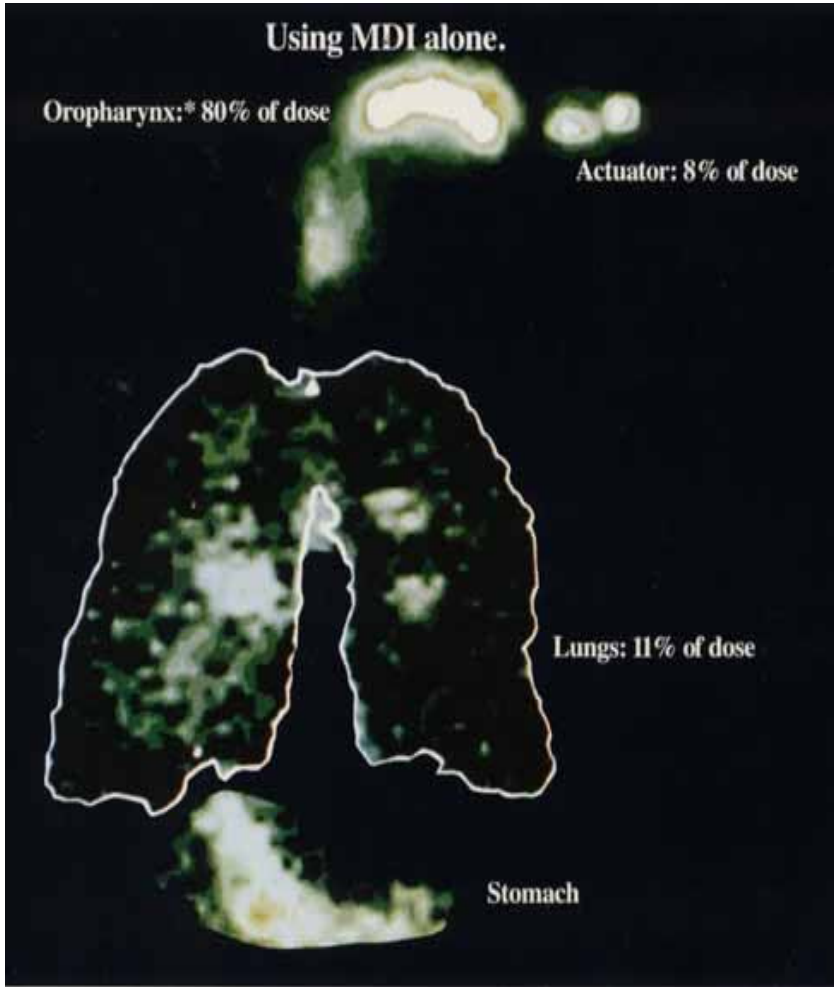
Table 1. Factors that may result in inconsistent medication delivery from VHCs.

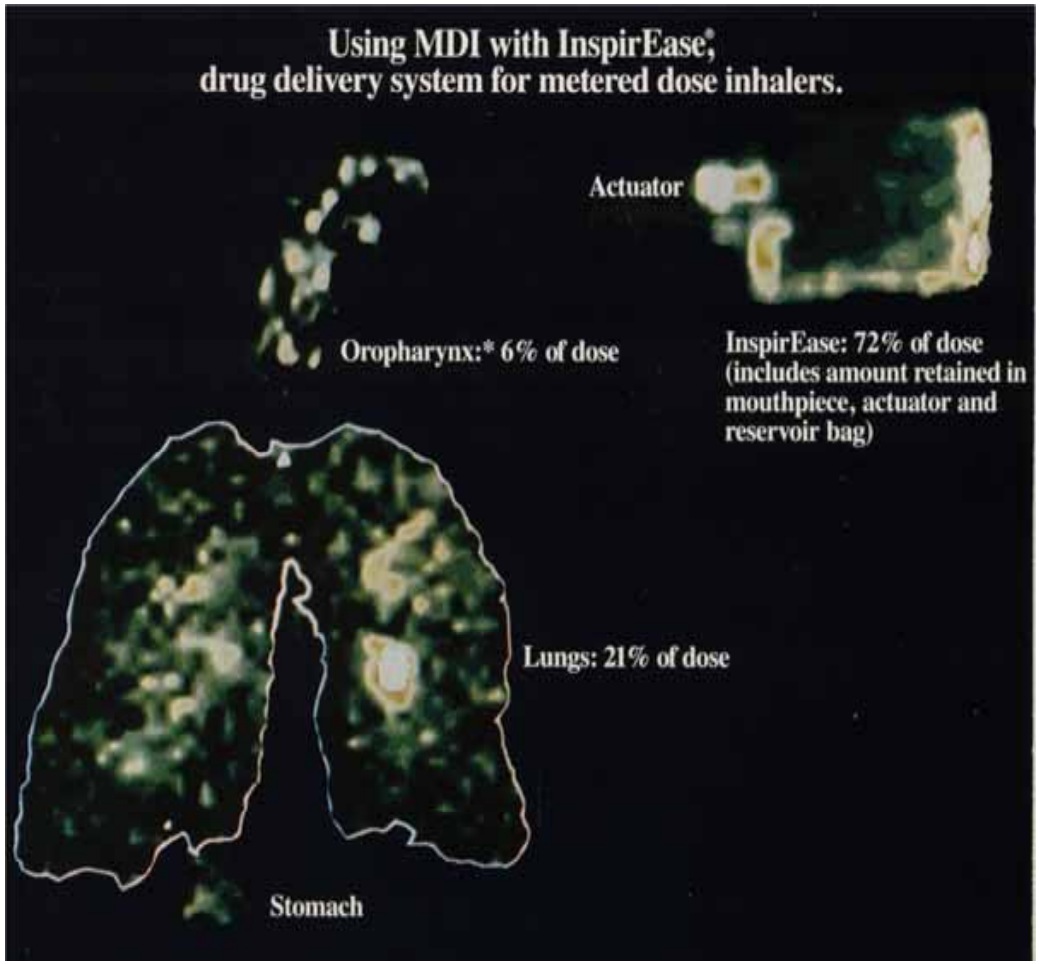
Device related	Patient related
1. Electrostatic charge – associated with both aerosol from the inhaler and interior surfaces of the VHC	1. Choice of appropriate VHC and patient interface (mouthpiece or facemask) – infant, child, adult
2. Inhalation valve function – most important with devices intended for use by infants whose inspiratory flow may not open a valve that has stuck closed	2. Patient inhalation modality
3. Size (volume) of VHC in relation to patient breathing pattern – more important for infants and small children	3. Disease modality and severity – may affect ability to use a particular patient interface
4. Facemask-to-face seal integrity – essential, especially for infants and small children	

VHC = valved holding chamber

Prim Care Resp J 2007; 16(4): 207-214

LUNG DEPOSITION: MDI ALONE VS INSPIREASE





Newman SP et al. Chest 1986;89:551-6

- No extra benefit in terms of delivery by the patients who follow the correct technique with MDI alone

Am J Respir Crit Care Med 1996; 153: 1636-40

- Problems –
  - electrostatic charge develops on inside of the chamber due to regular washing and drying → affects delivery of larger particles
  - New HFA based MDI have not been evaluated with presently available chambers
  - Because of the differences in the physical characteristics of particles generated by HFA based MDI drug delivered to the patient may be different
- Dry chamber using a non-static cloth or to let it air dry
- Use of non-electrostatic materials for chambers

DPI

Why were DPIs invented?

- Large number of patients had difficulty in using conventional MDI's
- Primarily because
  - Could not synchronize actuation & inspiration techniques
  - Faulty techniques led to decreased drug delivery → poor control of symptoms & compliance
  - Discontinuation of therapy

- CFCs considered to be unfriendly to the environment
- DPIs are essentially propellant free & "environment friendly"
- DPI's are breath-actuated & eliminate need for co-ordination of actuation & inspiration

DPI

- DPI consist of pharmacologically active powder as an aggregate of fine micronised particles in an inhalation chamber

- Aggregates are converted into an aerosol by inspiratory airflow through the inhaler generated by patient

DPI - Historical Aspects

- 1971 - Spinhaler
- 1988- Rotahaler

DPI

- Fraction of drug delivered to site of action→ 9% - 30% & varies among different commercially available products

Am J Respir Crit Care Med 1996; 153: 1636-40

- Flow of 60-90 L/min is generally required to be generated & vary among various available DPIs

- High humidity & rapid changes in temperature may affect de-aggregation & reduce fraction of delivered drug

Am J Respir Cell Mol Bioi 2000; 161: A35

DPI

- Single Dose Devices
  - Spinhaler, Rotahaler, Aerolizer, Handihaler, Revolizer
- Multiple Unit Dose Devices
  - Diskhaler
- Multidose Devices
  - Turbuhaler, Diskus
- Novalizer

DPI - Rotahaler

- Single dose, no counter
- Has to be loaded, with coloured half of rotacap down
- Uses larger amount of powder
- Lactose based → can taste the drug
- Can be washed

DPI - Diskus/Accuhaler

- 60 doses/ in a foil, with a reverse counter, Last 5 doses numbered in red
- Must be held in a level horizontal plane while loading and using
- Breathing into the mouth piece causes a lost dose
- Dose is felt because of lactose base
- Must be kept dry at all times

DPI - Turbuhaler

- 200 doses in a reservoir, reverse counter
- Fine, additive free dry powder
- To be kept upright during loading and horizontal during use
- Breathing into the mouth piece spoils that dose
- It is tasteless
- Must be kept dry

DPI - Novolizer

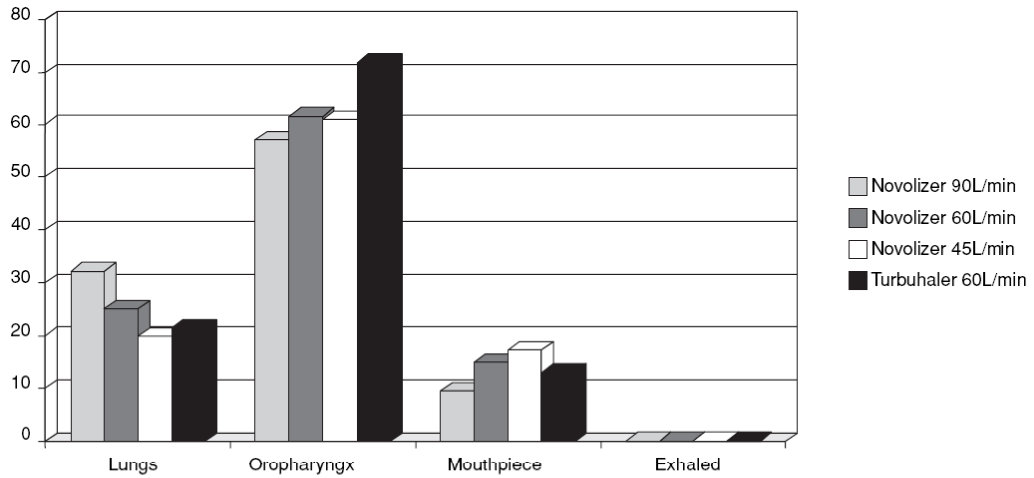
- Multi-dose DPI device which can be re-filled by replacement of cartridges
- Several benefits over other DPI devices
  - patient feedback mechanism
  - trigger flow valve and
  - low to medium intrinsic resistance that ensures that patient have high flow rates while using this device

Respir Med 2004; 98: S22-S27

- Particle size generated is independent of flow generated by patient
- Higher drug deposition at higher flow rates

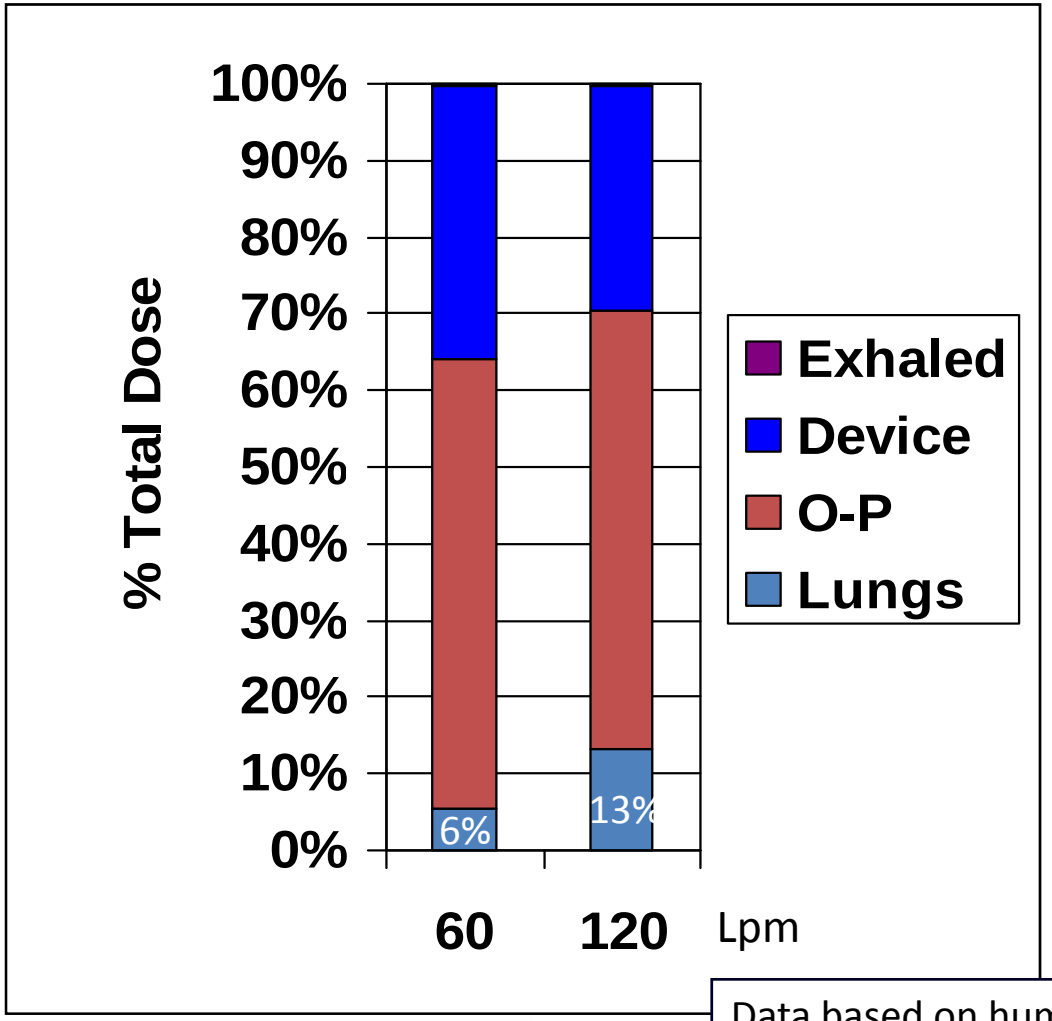
Eur Respir J 2000; 16: 178-83

DPI - Novolizer



Curr Med Res Opin 2005; 21(SUPPL 4)

Effect of different modes of inhalation on drug delivery from a dry powder inhaler



. Int J Pharmaceutics 1994;102:127-32

Data based on human deposition
With radiolabelling

AN IDEAL INHALER

- Dose reliability
- High dosing efficiency (> 10-20%)
- Small particle size < 5 microns
- Simple to use & handle
- Short treatment time
- Small size, easy to carry
- Multiple dose capability
- Resistance to bacterial contamination
- Durability
- Cost effective
- No ambient aerosol drug contamination
- Efficient for specific drug used
- Liked by patients!

Respir Care 2002;47(11):1257-75

- MDIs have lung deposition of 5–15% of delivered dose
- Current DPIs have similar efficiency
- Advantages over MDIs
  - breath-actuated & therefore require less coordination
  - CFC
  - Multidose DPIs have either a dose counter or indicator of remaining medication in inhaler
- Disadvantages
  - require moderate inspiratory effort to draw formulation from the device → some patients are not capable
  - limited number of drugs available in a multi-dose format
  - some drugs being available only in unit-dose formats
  - Unit -dose devices are perceived as complex and confusing for patients

Drug Topics 2005;4:48

Characteristics of the aerosol generators

	MDI	DPI	Nebuliser
Technique of aerosol generation	Propellant based	Patient driven flow	Bernoulli's principle/piezoelectric crystal
Particle size	1-10 µ	1-10 µ	Variable
Drug deposition	5-10%	9-30%	2-10%
Oro-pharyngeal deposition	Significant	Variable	Insignificant
Patient coordination	Required	Not applicable	Not required
Breath hold	Required	Not required	Not required
Patient generation of flow	Not required	Required	Not required
Amount of drug	Small doses on!y	Small doses only	Large doses possible
Contamination	No	No	Possible
Use for chronic therapy	Yes	Yes	Rarely
Use for emergency management	No	No	Yes
Use for intubated patients	Preferred	No	Second choice
Cost	Cheap	Cheap	Expensive

Indian J Chest Dis Allied Sci 2008; 50: 209-219

Summary

- Aerosol therapy has been cornerstone of management of obstructive airway diseases for > 50 years & have witnessed many advances in recent times

- Improved aerosol generators with different drug formulations are available but fraction of total drug eventually delivered still remains small

- There are advantages and disadvantages associated with various devices

- MDI with or without a valved spacer have emerged as preferred devices but require good coordination & may be inconvenient in some pt

- Breath-activated devices may require higher inspiratory flow rates and may be difficult for pt with limited capacities
- Choice of device depend on medication prescribed and the abilities of patient
- Patients need to be well informed & feel comfortable with use of chosen device
- Effective delivery of aerosol medication is primarily dependent on correct technique
- Essential for health professionals to keep up to date & proficient with all delivery systems