

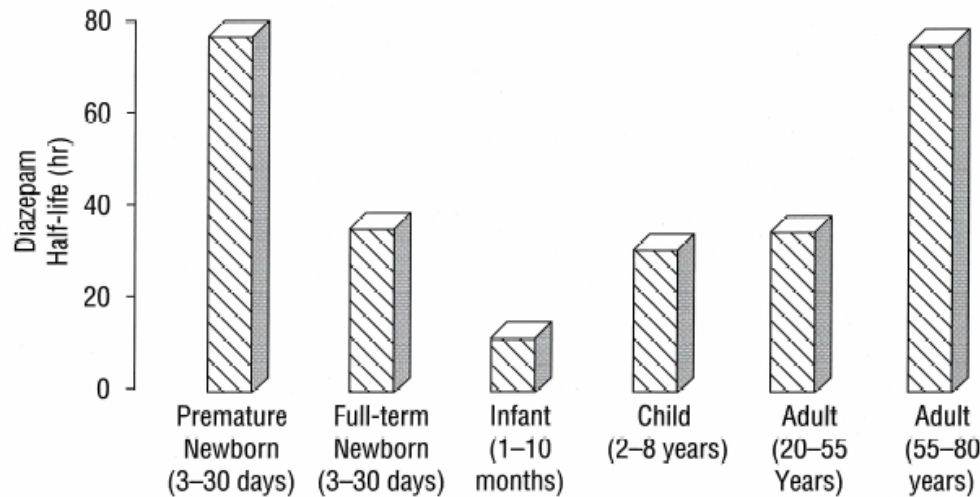
Do's and Don'ts - Practical Experience from Clinical Trials in Children

4th Annual Sweden Bio Clinical Trials Day

Staffan Edsbäcker

Clinical Pharmacology
AstraZeneca R&D Lund

Why clinical studies in children?

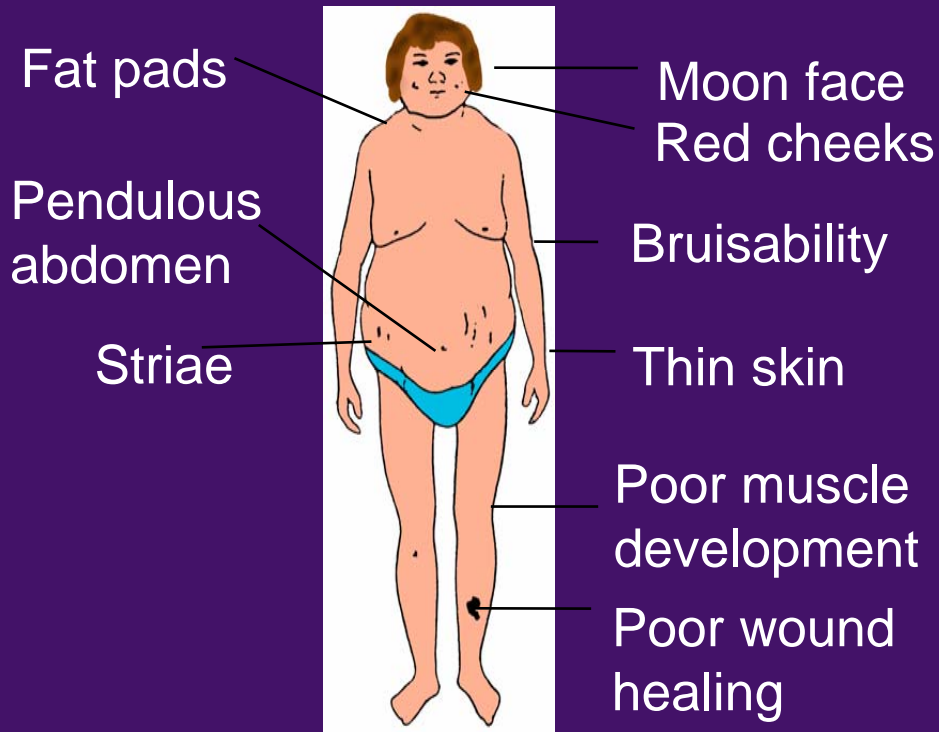


Klotz et al 1975

- PK (disposition, absorption) may differ
- Disease manifestation can differ
- Medical and regulatory demands
- Marketing aspects



Cushing's Syndrome



Height



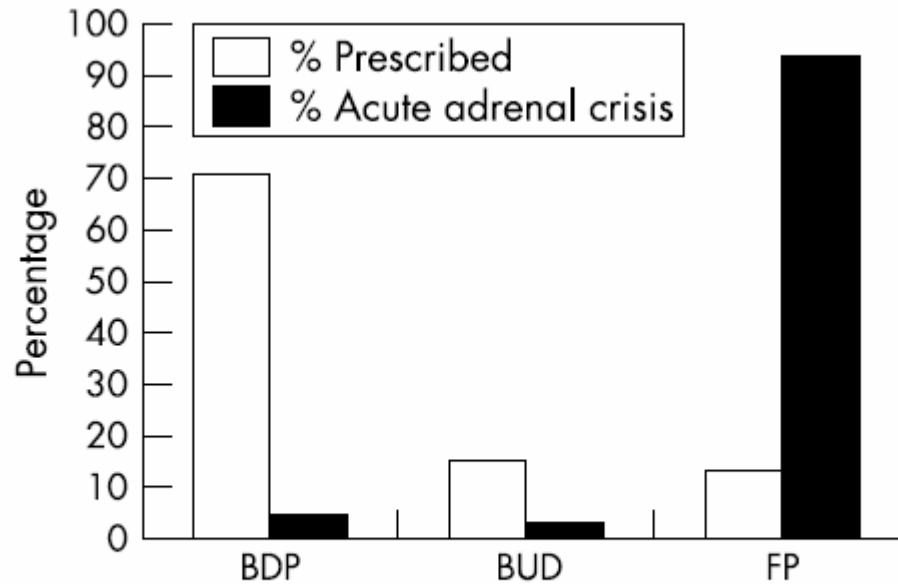


Figure 1 Percentage of prescriptions in the UK compared with percentage of cases of acute adrenal crisis reported in a UK survey.

Todd 2002

CURRENT PROBLEMS IN PH

THE latest edition of *Current Problems in Pharmacovigilance* (2001;27:9-15) published by the Committee on Safety of Medicines and the Medicines Control Agency (and available at www.mca.gov.uk) includes the following recommendations:

High dose fluticasone warning

Product information for inhaled fluticasone (Flixotide) products is being updated to highlight the risk of systemic adverse events. The new advice includes a recommendation to titrate to the lowest effective dose. In addition, only specialists should prescribe doses above 500µg twice daily. GlaxoSmithKline said that the new advice will be included in the product information for Flixotide by the end of this year.

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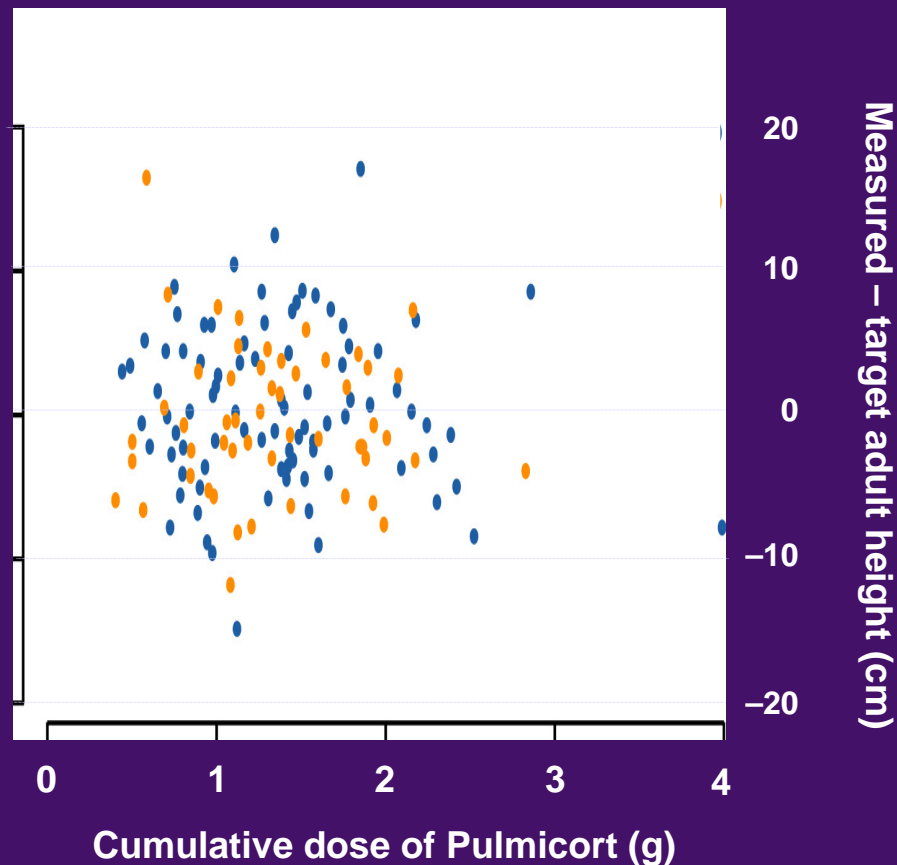
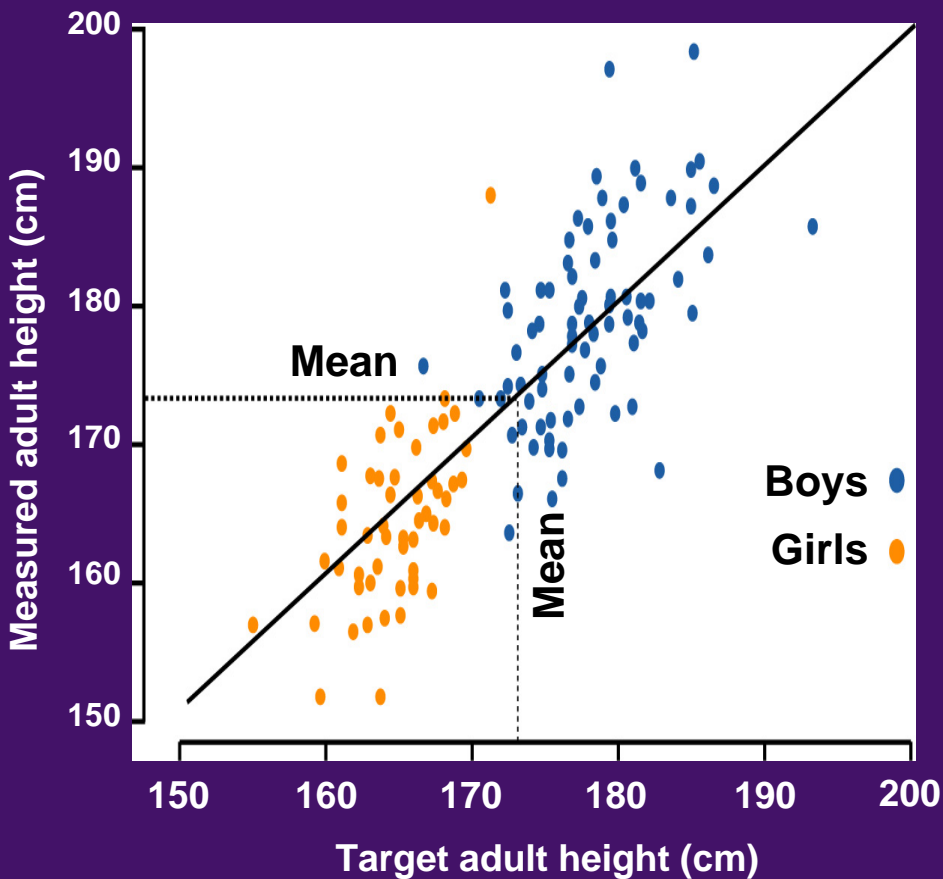
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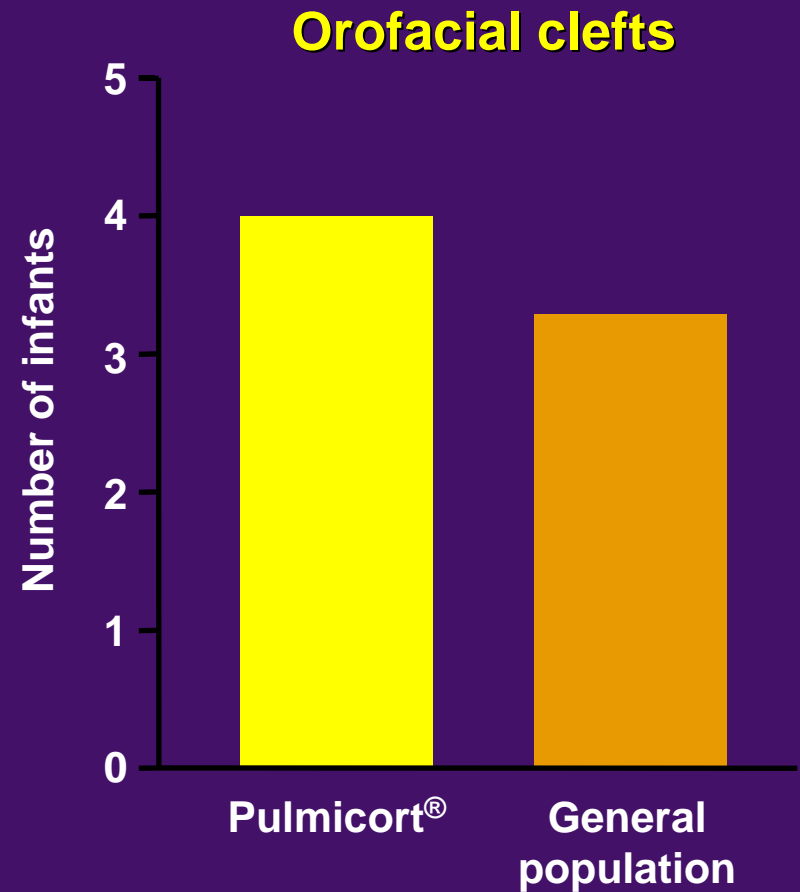
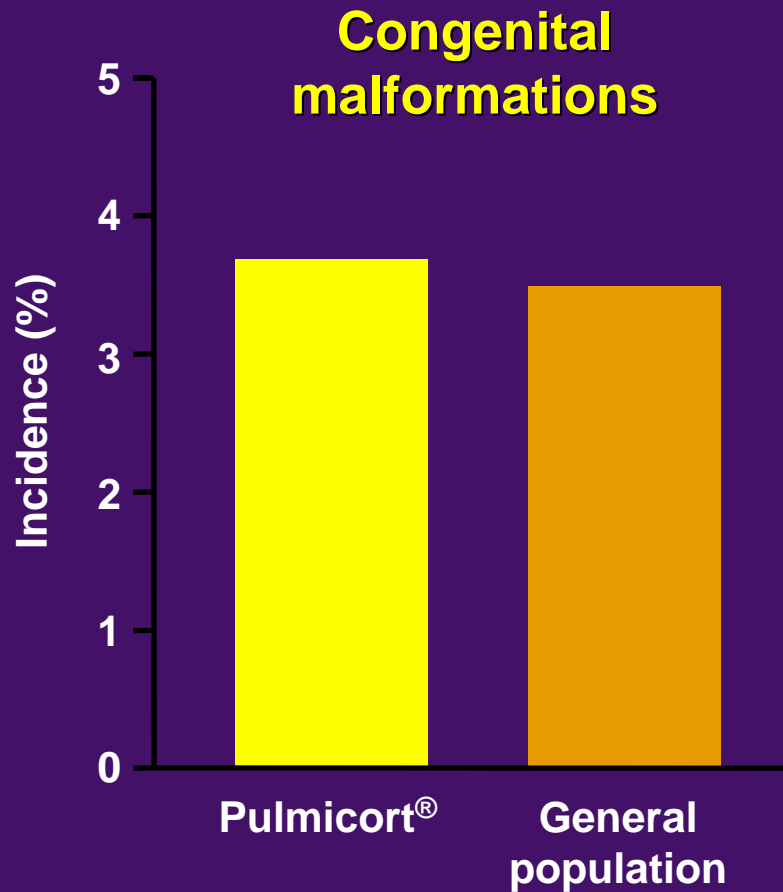
One Year Growth in Prepubertal (<9 yrs) Children

	<i>Inhaled</i>		<i>Intranasal</i>	
	Dose (µg/day)	Δ (cm/year)	Dose (µg/day)	Δ (cm/year)
Fluticasone	100	0.6	200	0.14
Budesonide	500	0.5	64	0.27
BDP			336	1.45

Pulmicort and Final Height



Frequency of Congenital Malformations



Pulmicort in Children – Clinical Documentation

-Safety

- Long term

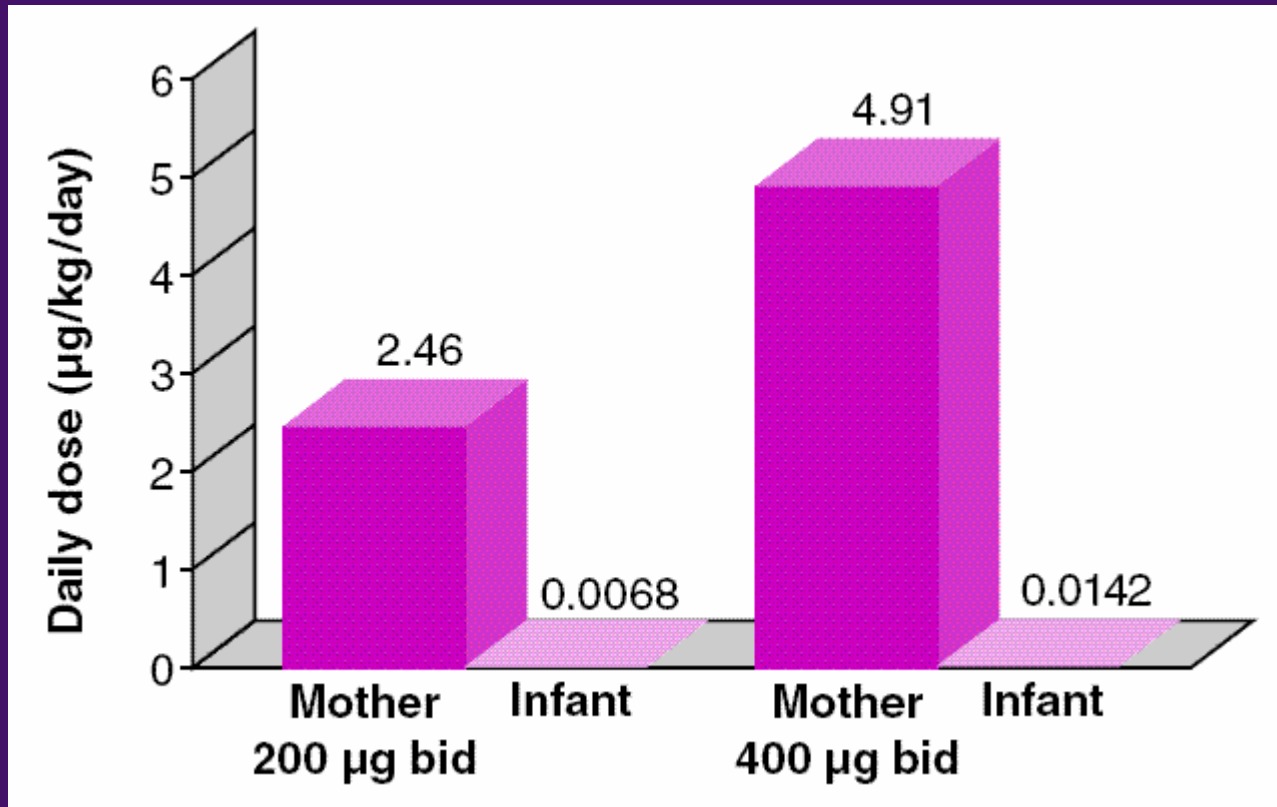
Bone Mineral Density
Growth
ACTH stimulation test
Ocular
Pregnancy

- Short term

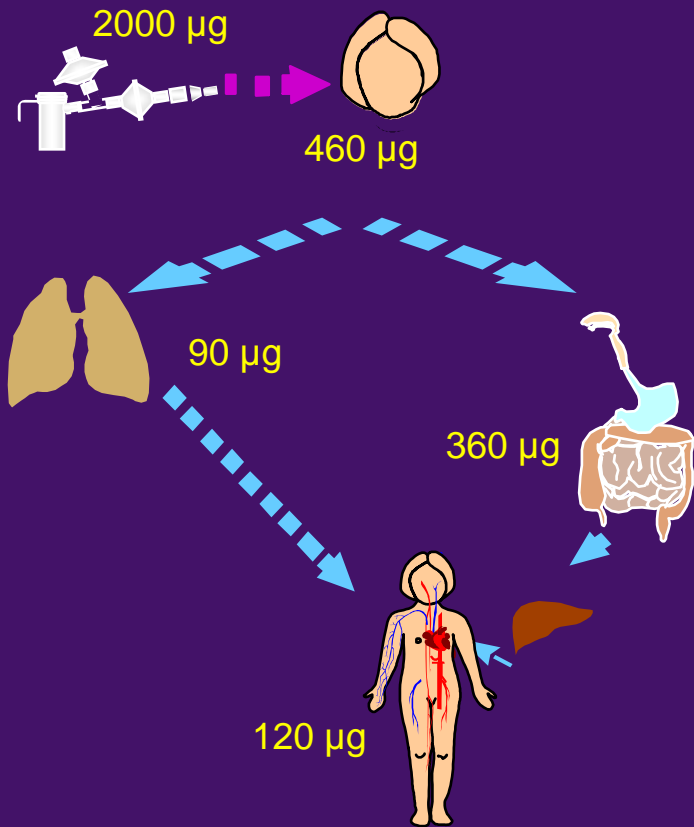
Cortisol
Lactation
Pharmacokinetics



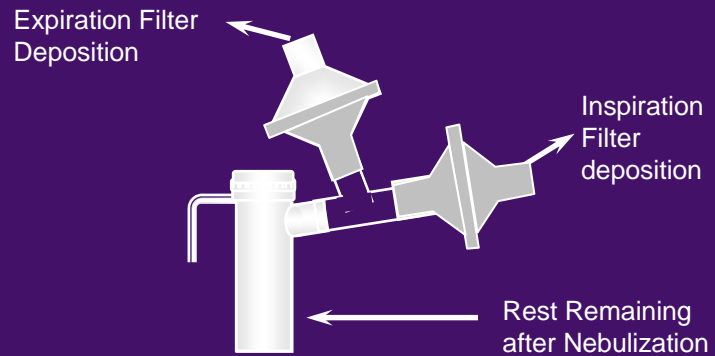
Budesonide and Lactation



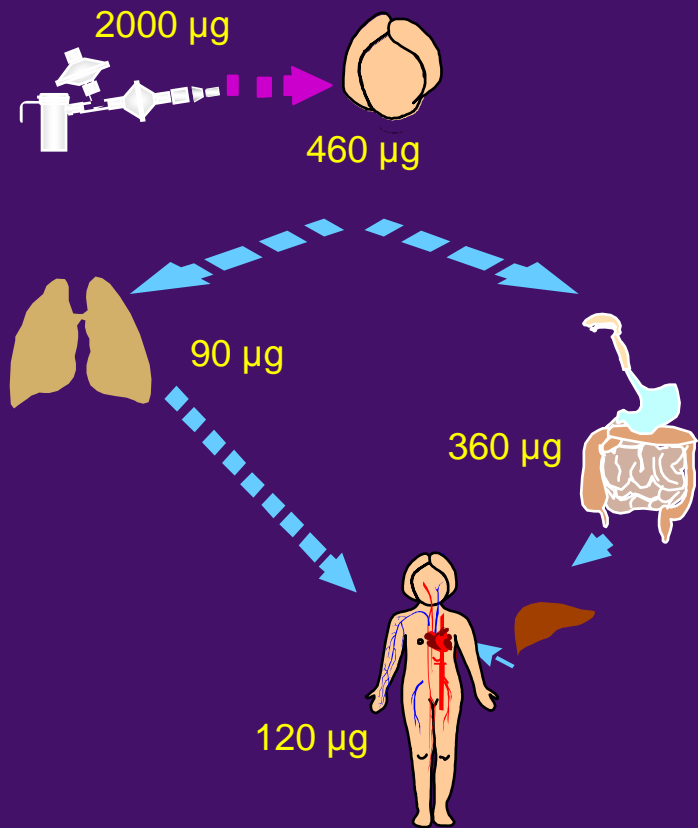
Fate of Pulmicort (budesonide) Respules



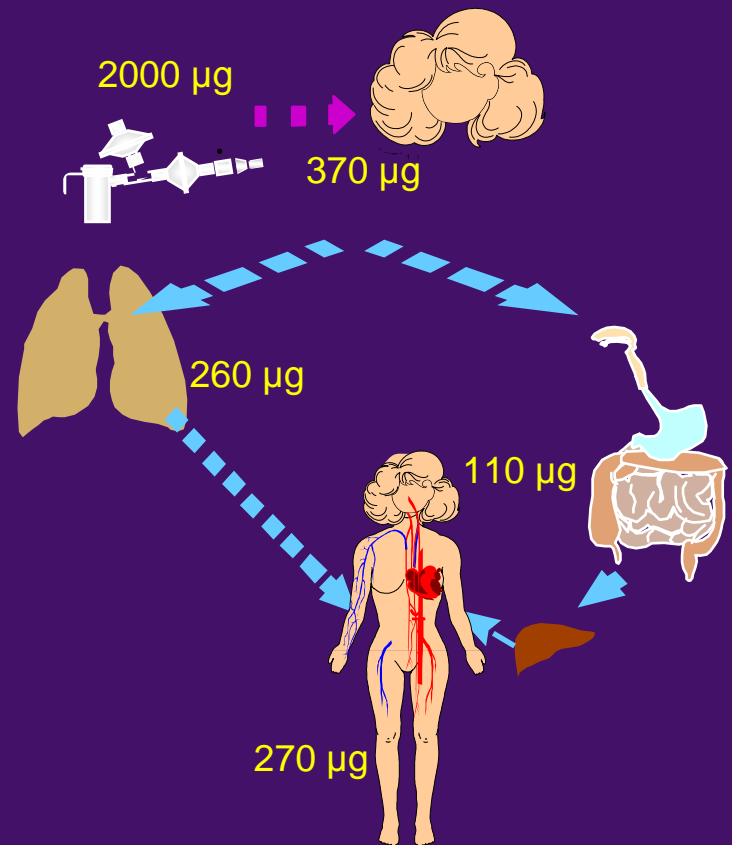
6 year old child



Fate of Pulmicort (budesonide) Respules



6 year old child



adult

Pharmacokinetics of Budesonide in Mild Asthmatics

Using Pressurized Metered Dose Inhaler with Spacer



- **Treatment**

- pMDI 2 x 200 μg inhaled via Nebuchamber
- 2-3 yrs using face mask
- 4-6 yrs and adults used mouth piece and nose clip

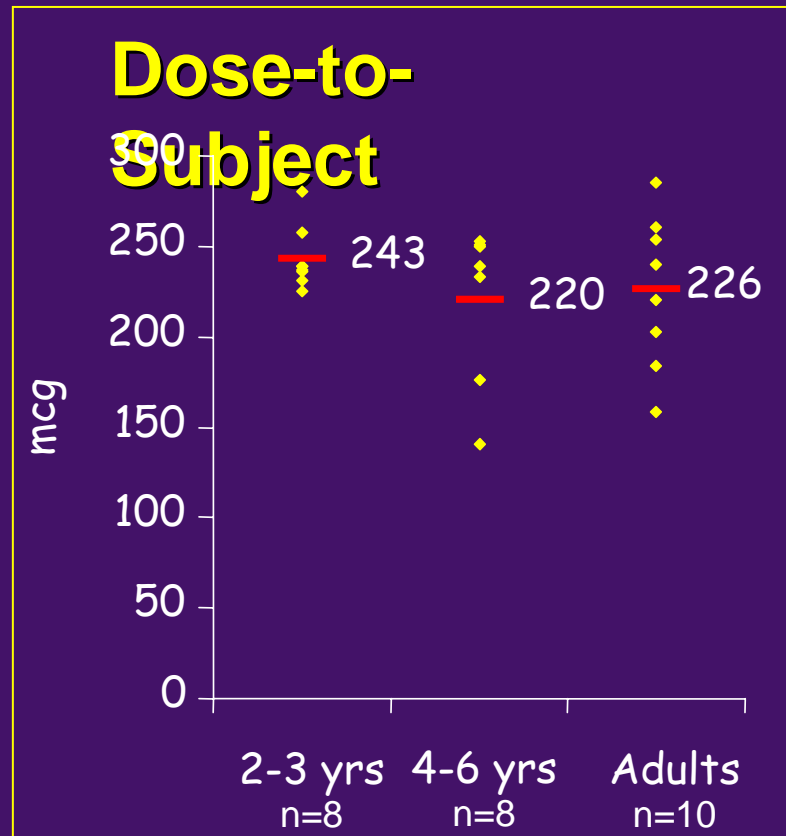
Pharmacokinetics of Budesonide in Mild Asthmatics

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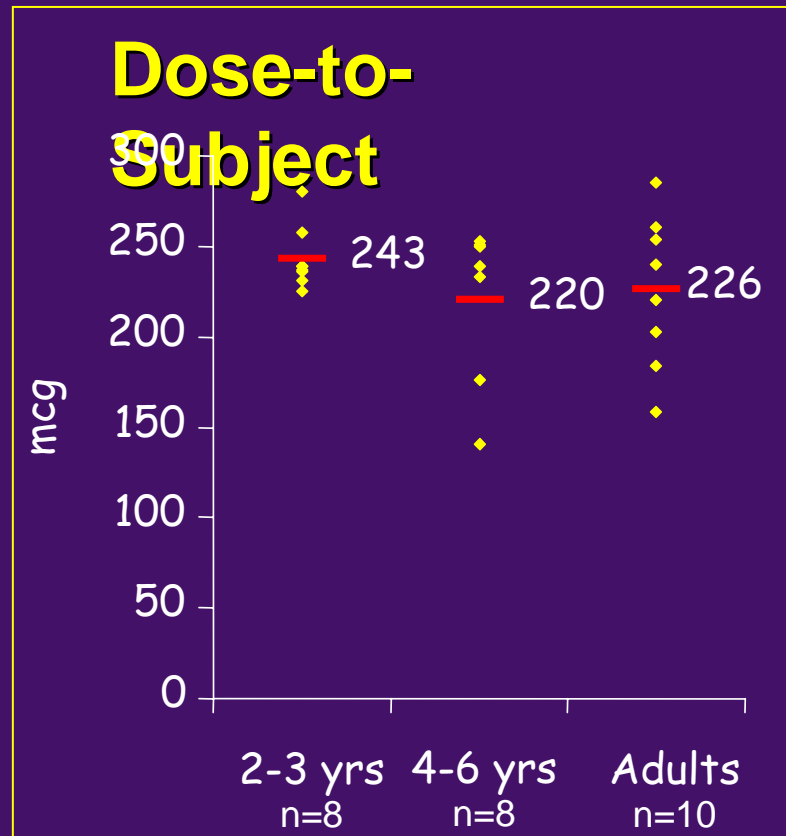


- **Treatment**

- pMDI 2 x 200 µg inhaled via Nebuchamber
- 2-3 yrs using face mask
- 4-6 yrs and adults used mouth piece and nose clip

- **Results**

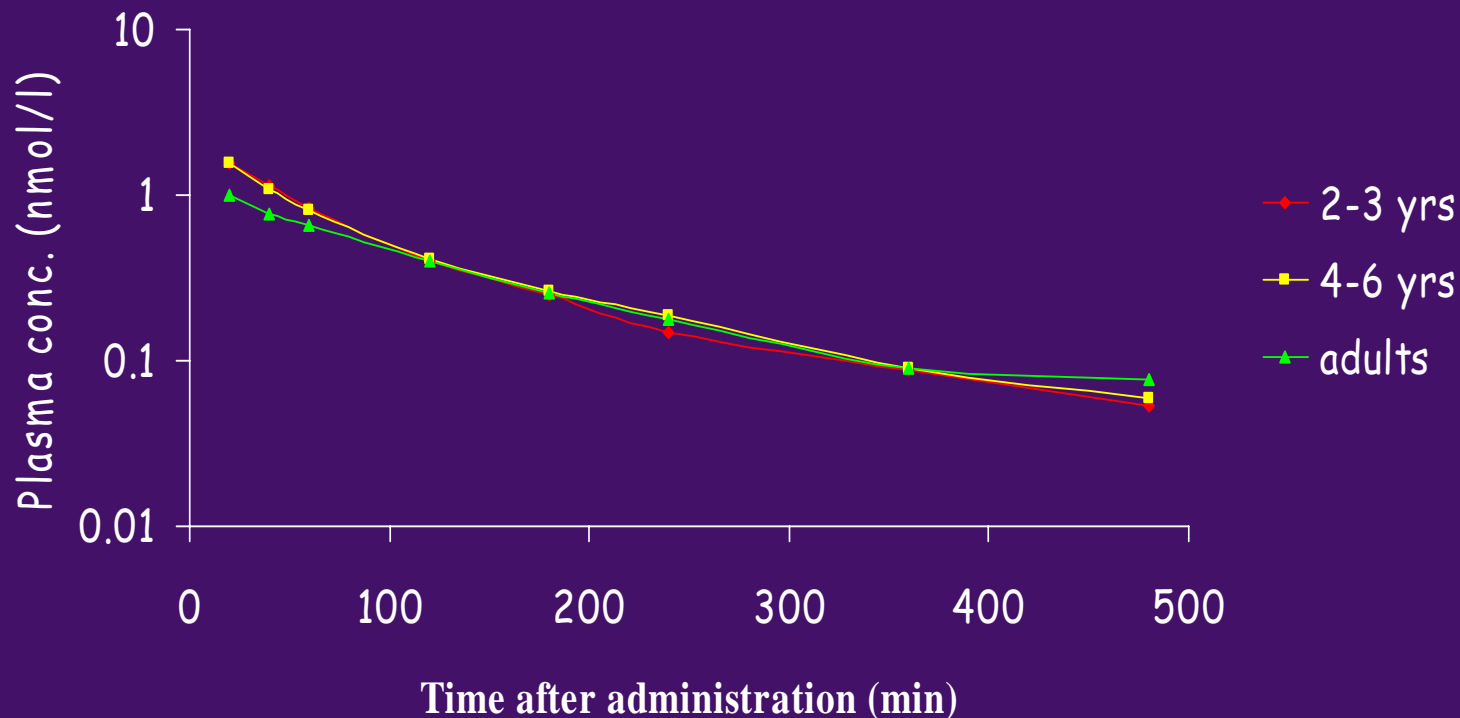
- No significant differences between age groups
- Nebuchamber output unaffected by the age of the patient



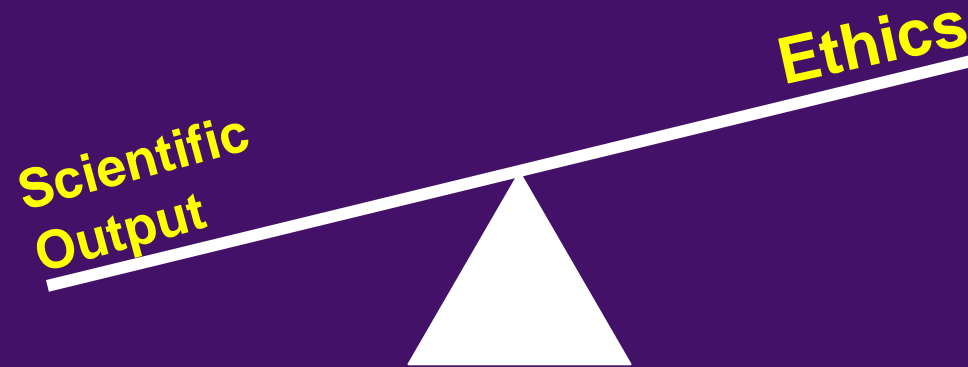
Pharmacokinetics of Budesonide in Mild Asthmatics

Using Pressurized Metered Dose Inhaler with Spacer

P-Budesonide



Pediatric Studies



Blood Sampling

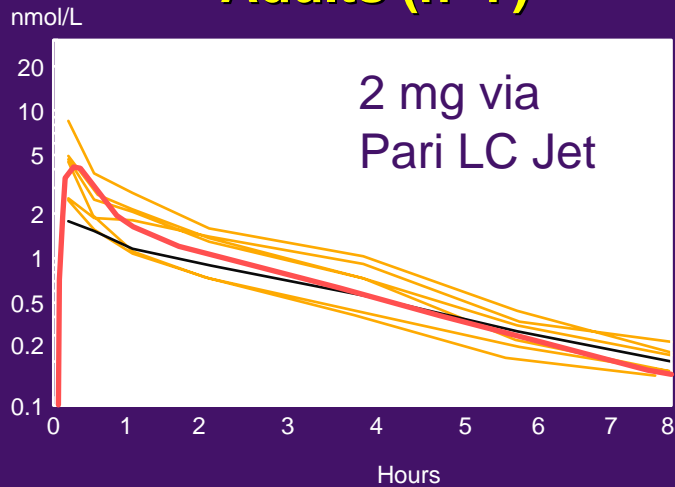


Budesonide Nebulizing Suspension

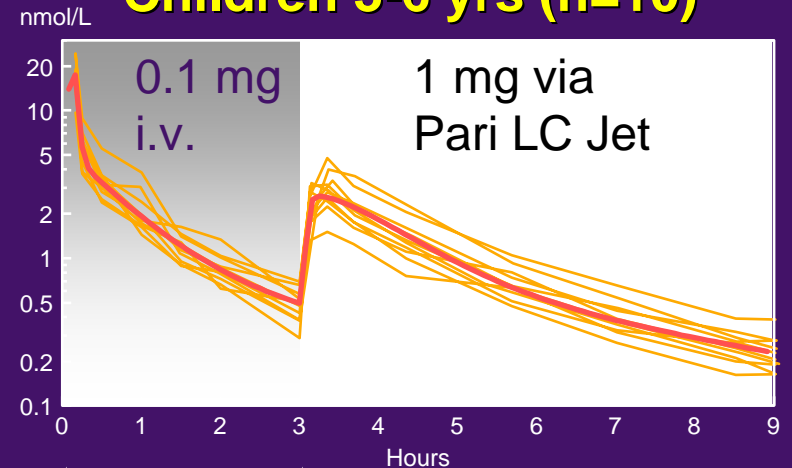
semi-simultaneous iv and inhaled doses

P-Budesonide

Adults (n=7)



Children 3-6 yrs (n=10)

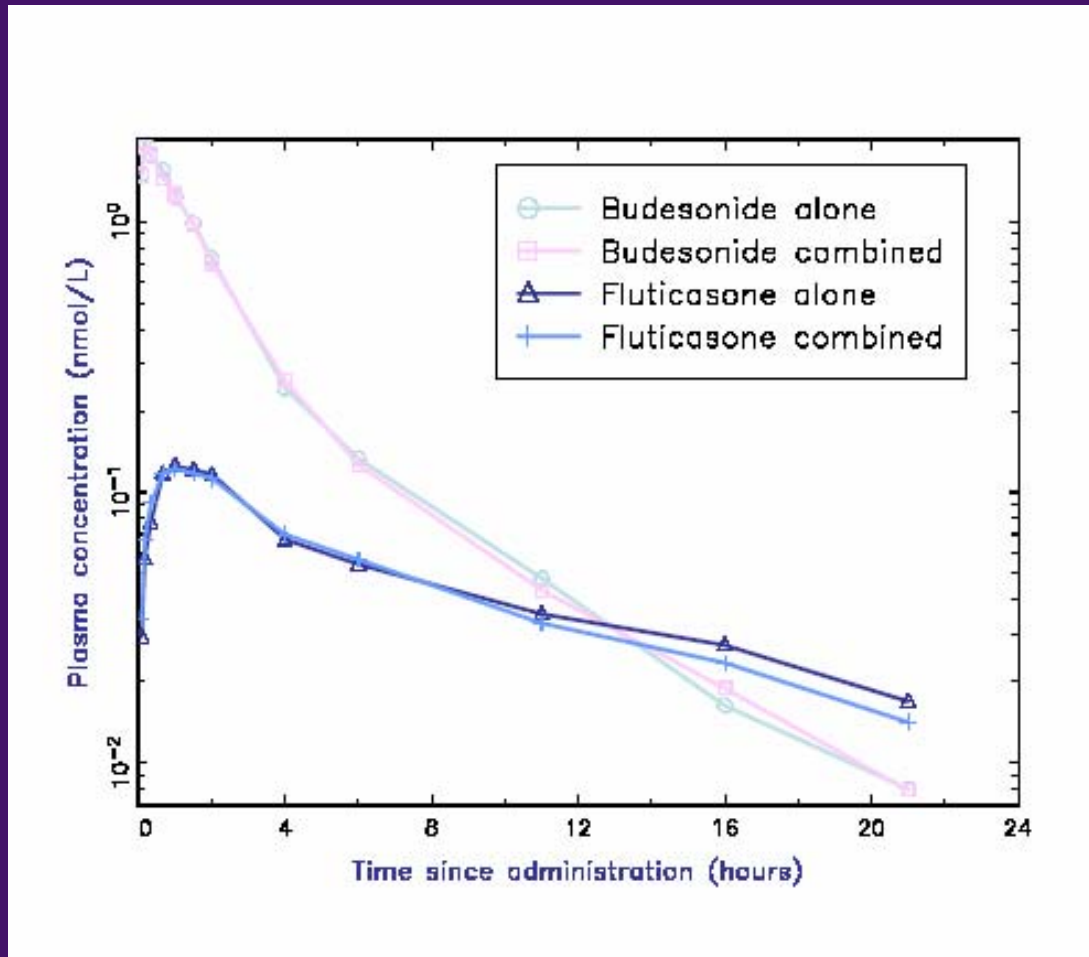


i.v.
dose

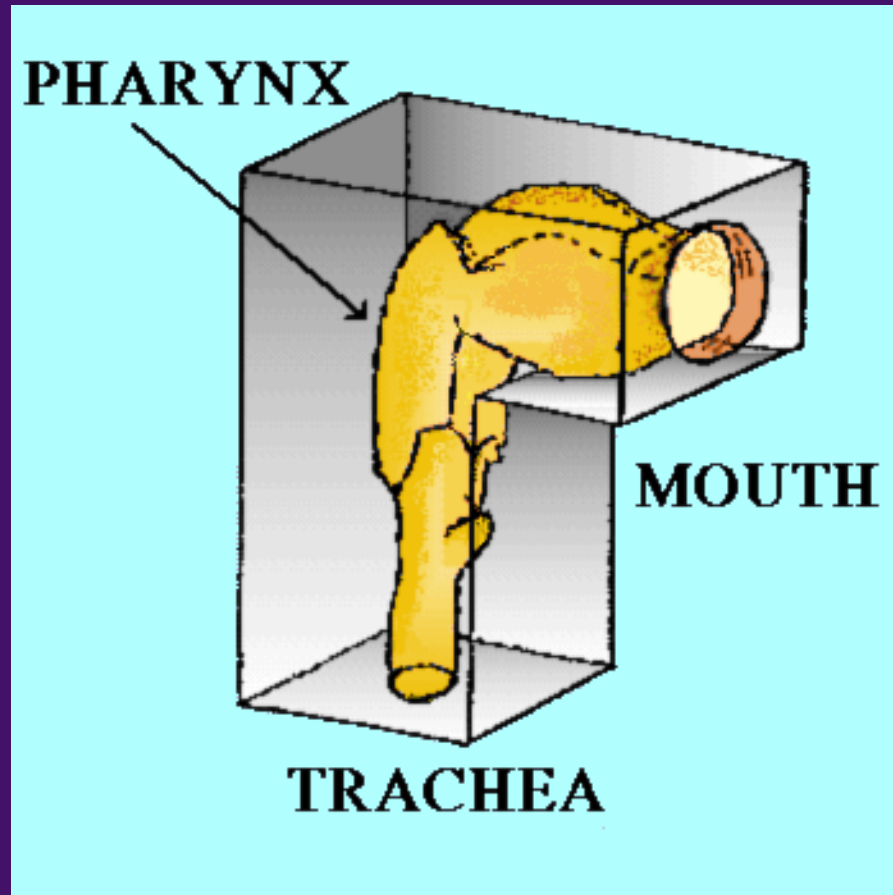
inhaled
dose

Agertoft et al 1999

Simultaneous dosing

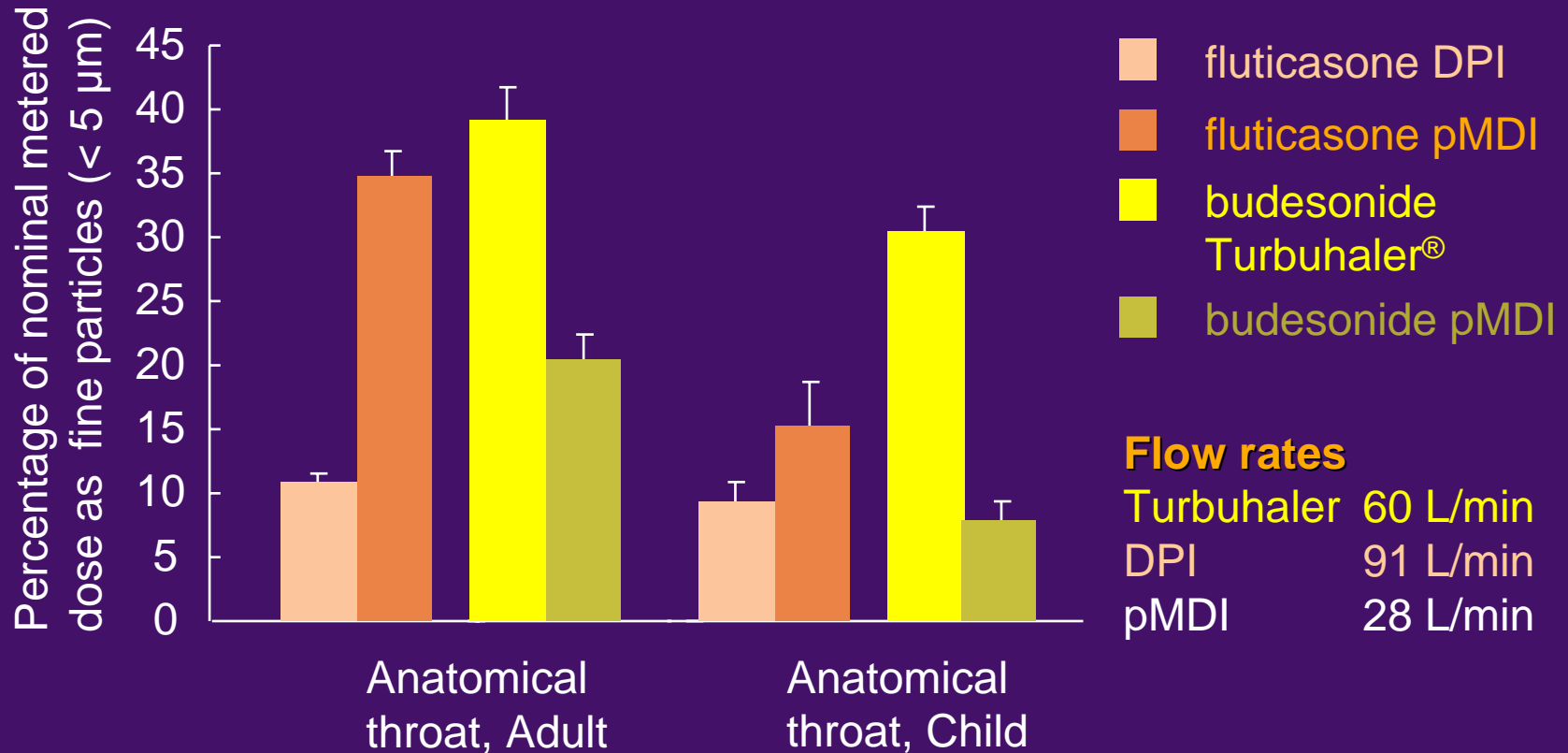


Anatomical Cast of Throat



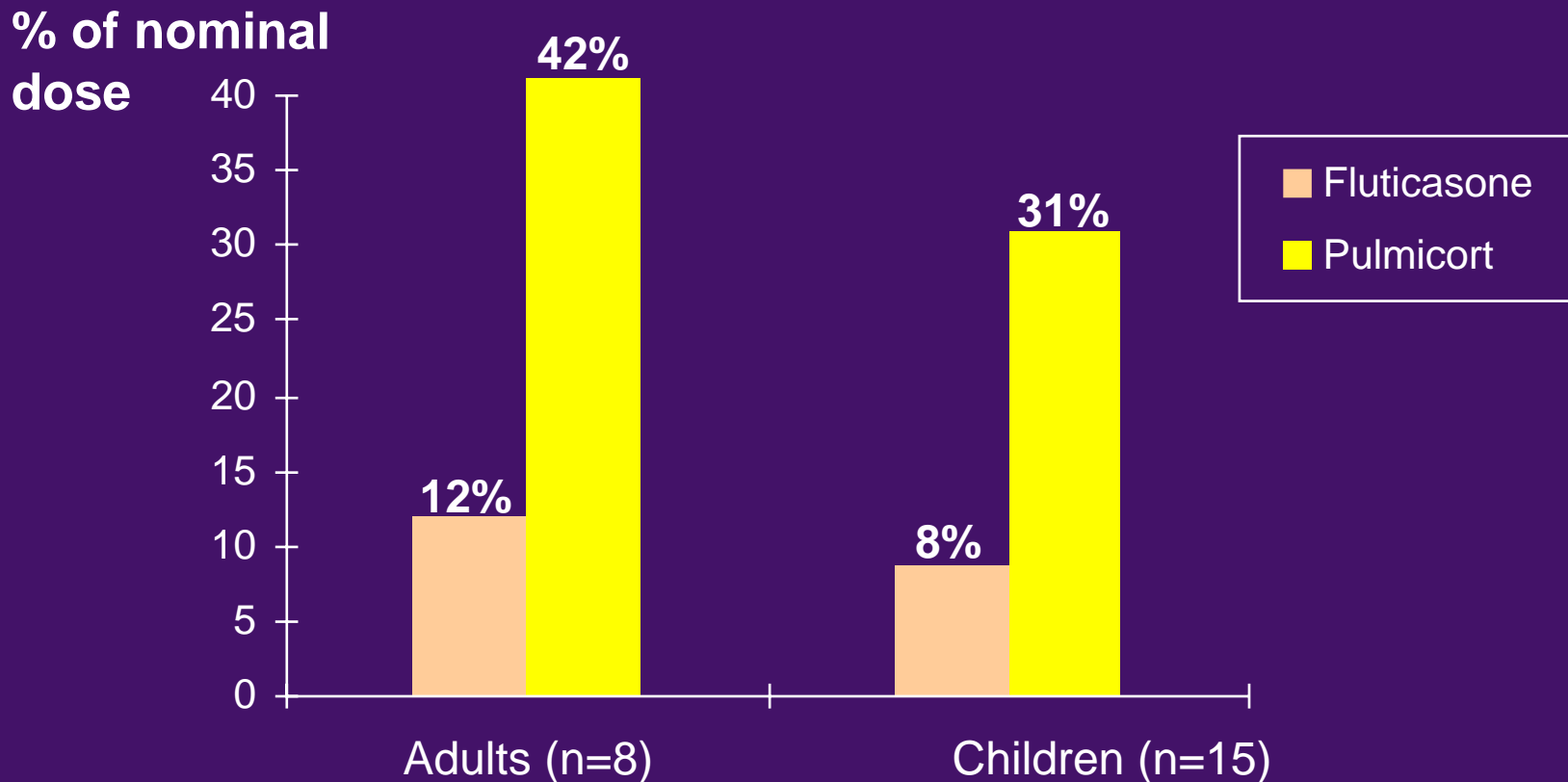
Fine Particle dose of Fluticasone and Budesonide

Andersen sampler with different inlet throats

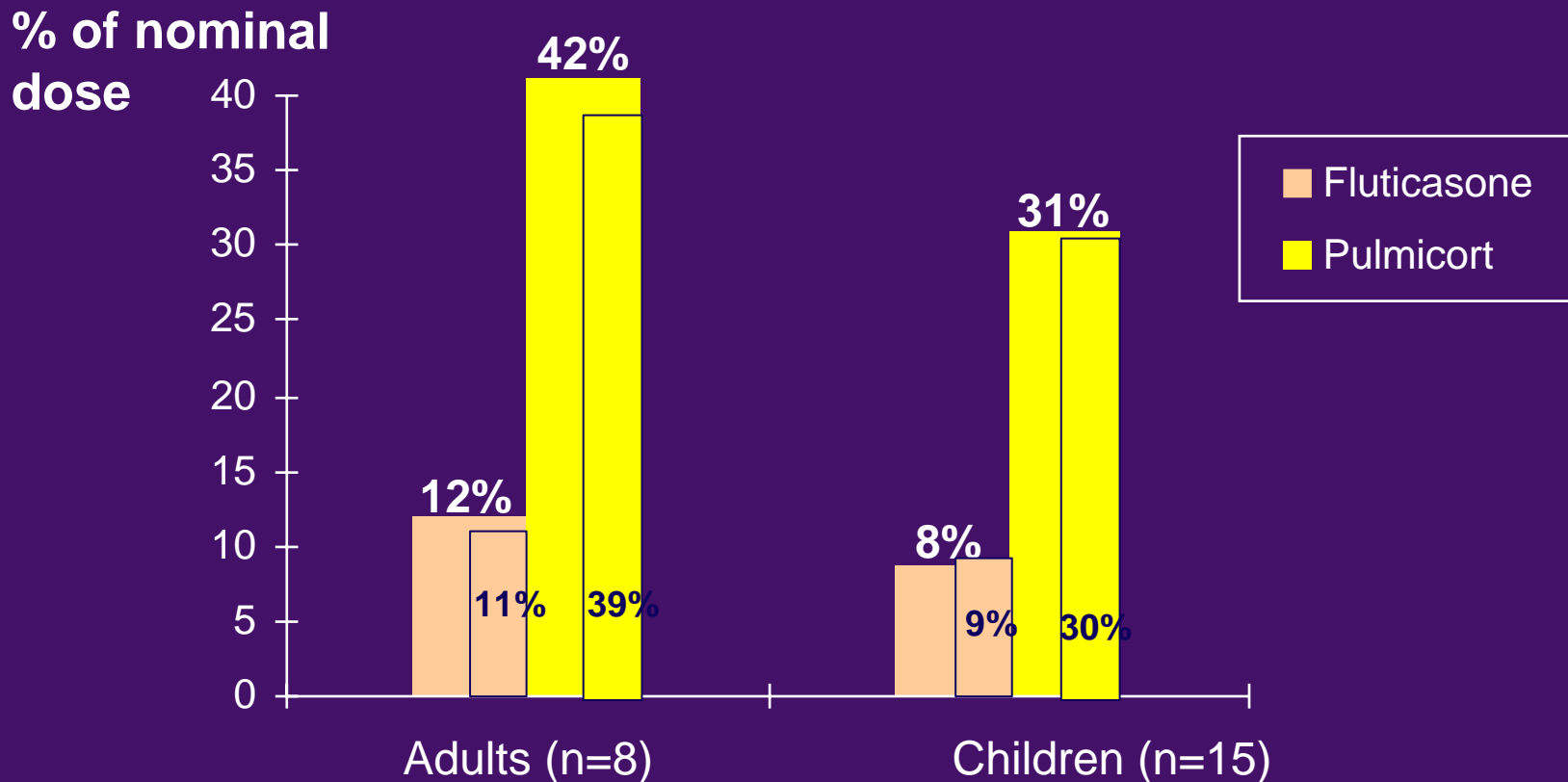


Berg, E. 1995; Olsson, B 1995

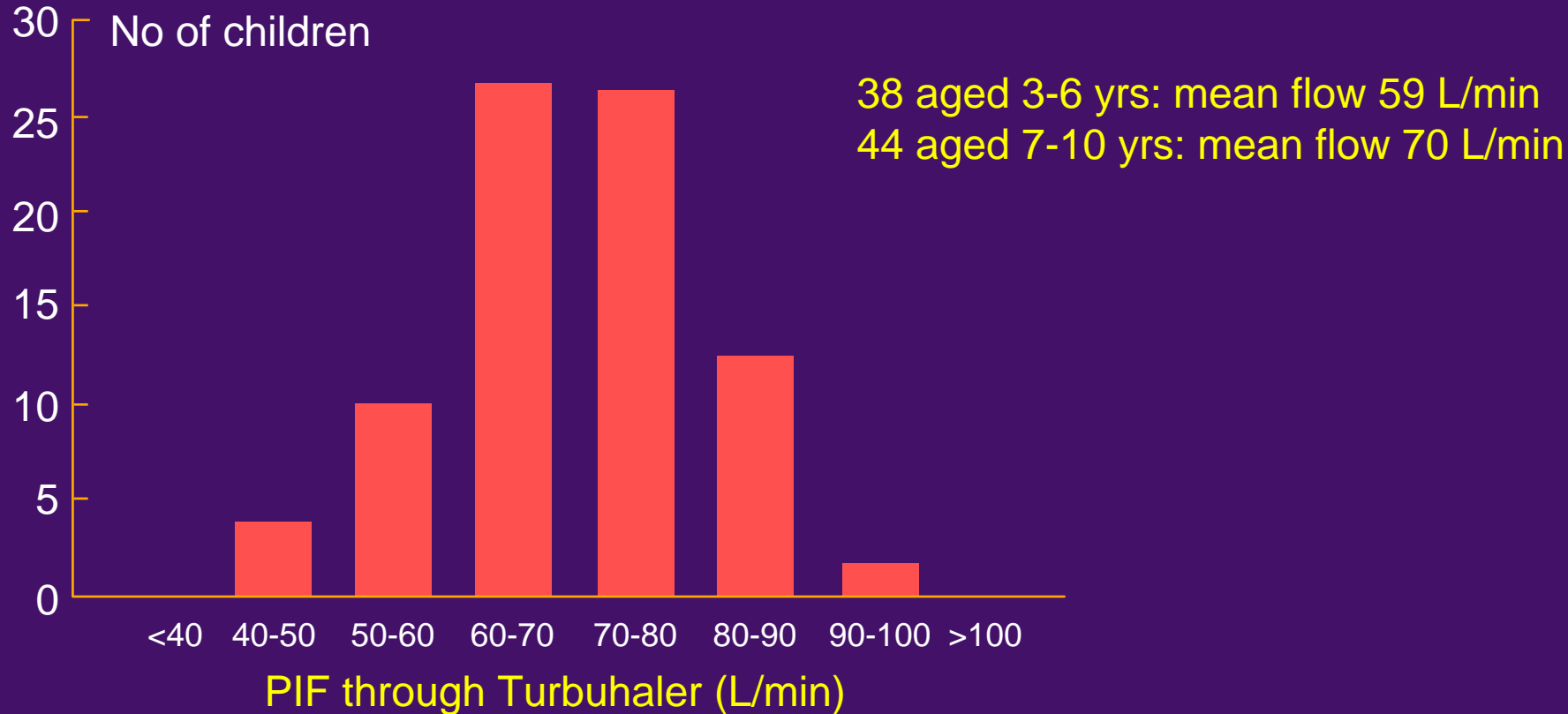
Lung Deposition in Asthmatics Inhaling Steroids via Dry Powder Inhalers



Lung Deposition in Asthmatics Inhaling Steroids via Dry Powder Inhalers



Peak Inspiratory Flow (PIF) through Turbuhaler in Children with Asthma



Pulmicort in Children – Clinical Documentation

-Safety

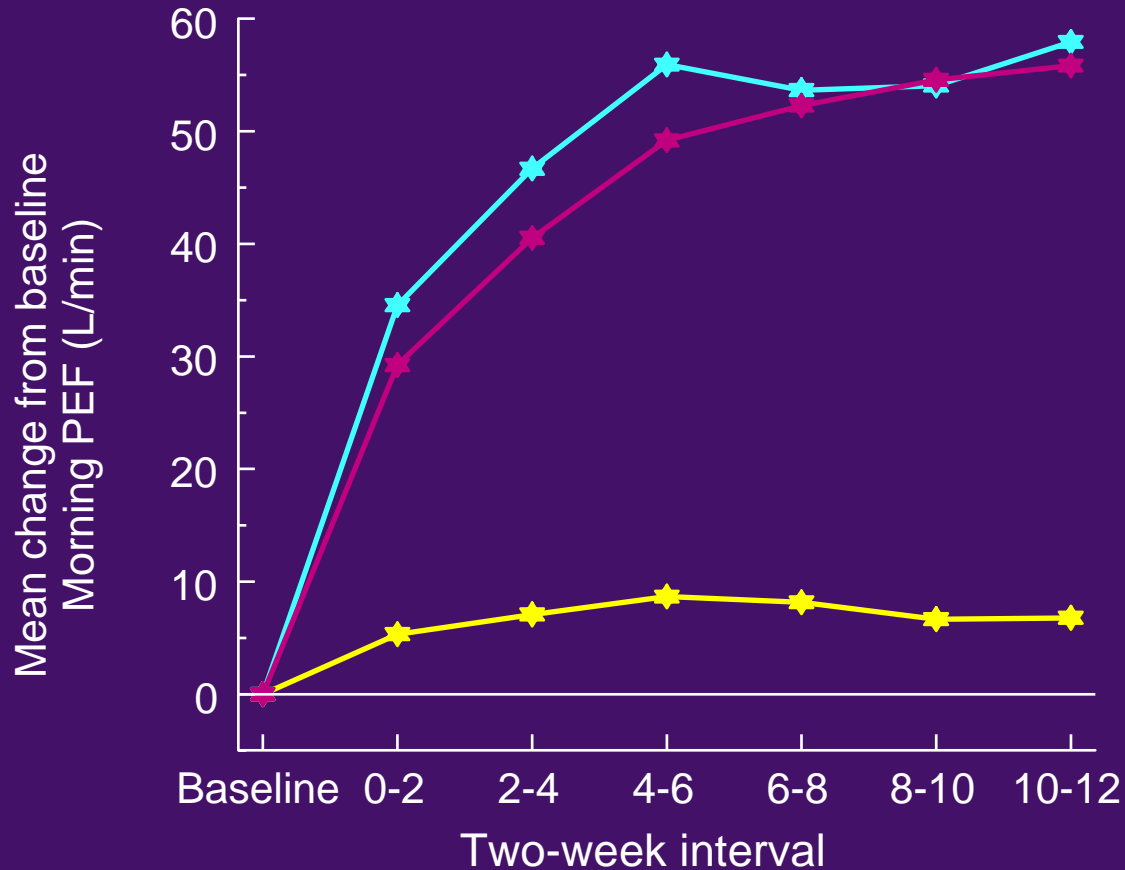
- Long term
 - BMD
 - Growth
 - HPA
 - Ocular
 - Pregnancy
- Short term
 - HPA
 - Lactation
 - PK

- Efficacy

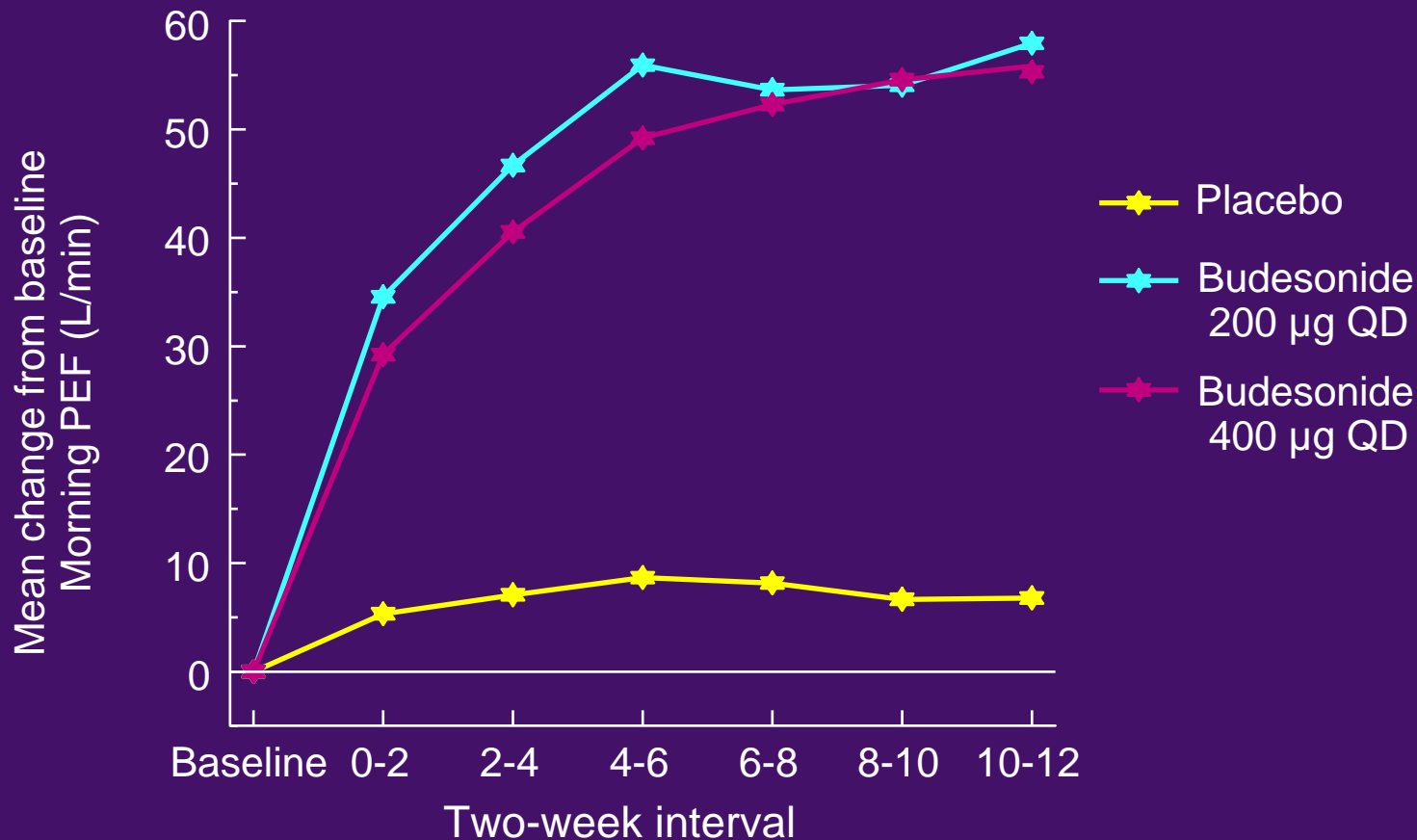
- Long term
 - Lung function
 - Exacerbations
 - Hospitalisations
- Short term
 - Lung function
 - Deposition



Two doses of an inhaled steroid vs placebo in stable asthma

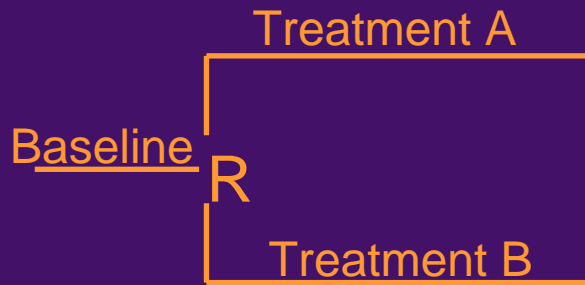


Two doses of an inhaled steroid vs Placebo in stable asthma

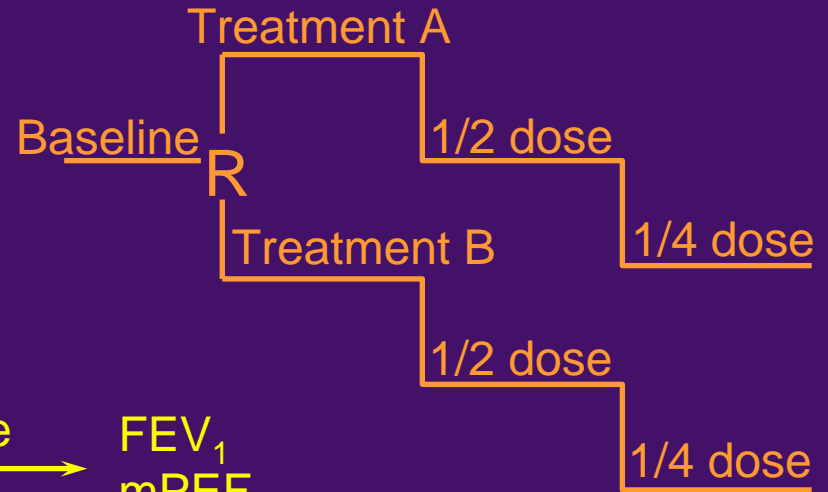


Study design

Study design 1 dose/concentration- controlled



Study design 2 effect-controlled



FEV₁
mPEF
symptoms $\xrightarrow{\text{Change}}$ FEV₁
mPEF
symptoms

Clinical Trials in Children – examples of Do's



- Maximize benefit vs. burden
 - Blood sampling
 - Semisimultaneous designs
 - Collect multipurpose samples
 - Pool samples
 - Use indwelling catheters (with topical anesthesia)
 - Develop assays requiring small blood volumes or (if possible) urine or saliva
 - Substitute, if possible, *in vivo* with *in vitro/ex vivo* experiments
 - Lung deposition
 - Trial designs
 - Have to be discriminative
 - Ensure authority buy-in

Clinical Trials in Children – examples of Don'ts

- Do not neglect informed consent and treatment benefit issues
- Do not assume mg/kg is valid dosing approach
 - When efficacy/safety is poorly related to weight
 - When PK/PD is nonlinear
 - When effect is topical
- Do not assume scarce PK sampling or truncated AUC designs will be successful – get authority buy-in
- Do not assume compliance in safety studies
- Do not assume capsules can be swallowed
- Do not exceed recommended maximum blood sample volume

