Case Examples: Extrapolation of Efficacy for GERD in Pediatric Patients

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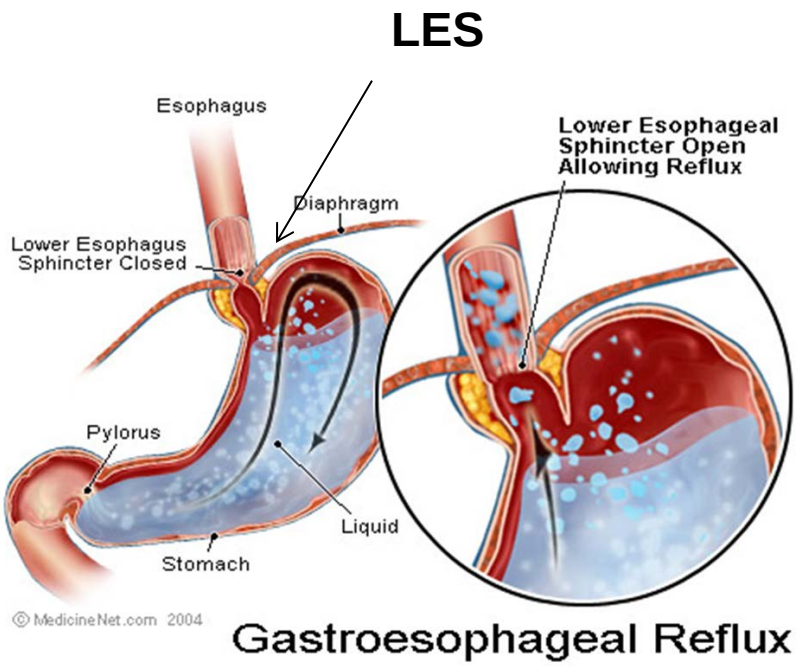
Case examples: Proton Pump Inhibitors

- Nexium® (esomeprazole)
- AcipHex® (rabeprazole)

  - Similar E-R relationship to support the extrapolation and the dosing in infants
  - PK guided dosing
  - Adult dose to match

Gastroesophageal Reflux (GER)

- Passage of gastric contents into the esophagus, with or without regurgitation and vomiting
- Normal physiological response to gastric distention
- Common in infants whose lower esophageal sphincter (LES) is immature
  - LES generally matures by the age of 1 year old



Gastroesophageal Reflux Disease (GERD)

- Symptoms or complications of GER
- Caused by exposure to acid
- Due to weak LES muscle

- Symptoms
  - Dry chronic cough, wheezing, nausea, vomiting and pain in the chest or the upper part of the abdomen

- Mucosal injury in the esophagus by the refluxate
  - Erosive Esophagitis (EE)
  - Non-erosive GERD (NERD) without mucosal injury
    - Symptomatic GERD

GERD in children

- Pathophysiology of GERD similar between adults and pediatric patients ≥ 1 year old
  - Suboptimal function of LES
  - Chronic exposure to acidic refluxate to damage esophageal mucosa

- PPIs approved for GERD in pediatric patients
  - To reduce gastric acid production
- Gastric acid secretion in the first day of life
  - Extrapolation of efficacy has been accepted

Extrapolation of efficacy for GERD in infants

- Extrapolation of efficacy has been utilized for GERD in pediatric patients ≥ 1 year-old

- Infants > 1 month old and < 1 year old*
  - Symptomatic GERD
    - Extrapolation is inappropriate
  - Disease not well-defined
  - Likely different pathophysiology e.g. non-acid related
  - Efficacy trials failed to demonstrate clinical benefit of PPIs

  - Erosive Esophagitis associated with GERD
    - Caused by exposure to acid
    - Extrapolation is reasonable with supporting PK and PD data

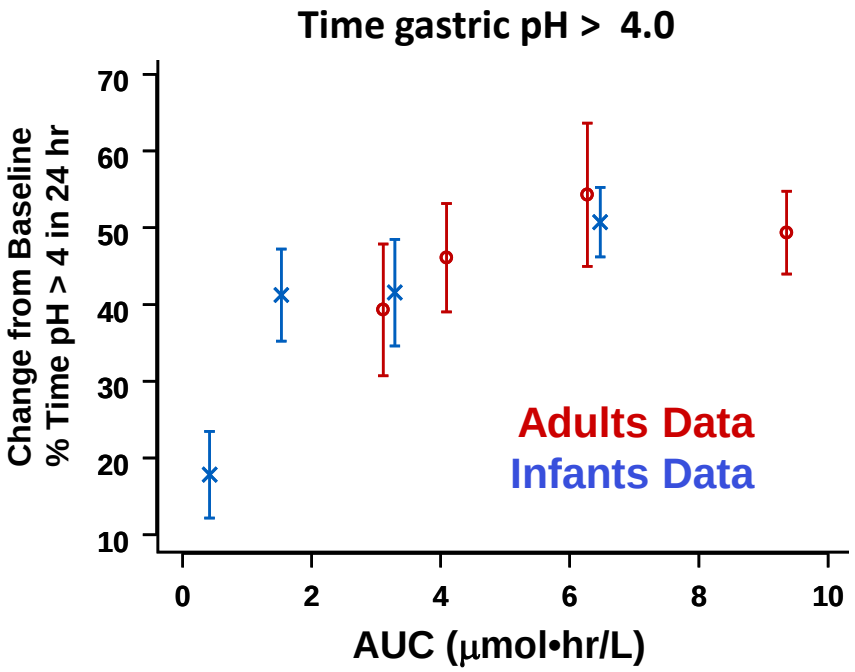
*** GIDAC:** Gastrointestinal Drugs Advisory Committee meeting on Nov. 5, 2010

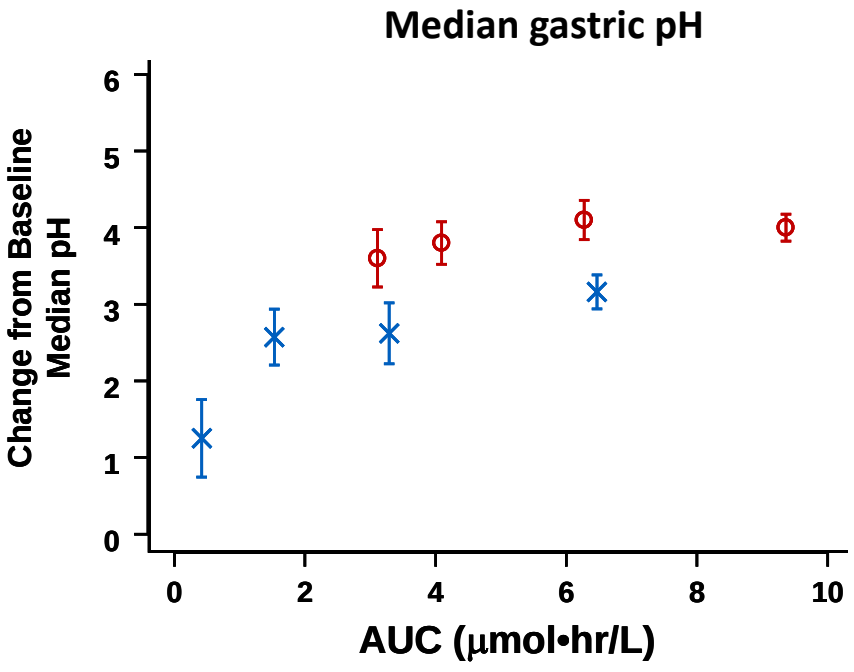
Nexium® (esomeprazole) : Studies to support dosing in pediatric patients

Age	Oral Esomeprazole	I.V. Esomeprazole
Indication	Symptomatic GERD Healing of EE	GERD with EE
Adults	Clinical trials for healing of EE and symptomatic GERD (DB, R, controlled)	Similar PD effects on suppression of acid outputs with oral esomeprazole[1]
12 to 17 years old	PK[1], safety	PK[1]
1 to 11 years old	PK[1], safety Supportive healing of EE	PK[1]
Infants (1-11 months old)	Efficacy trial for symptomatic GERD failed PK[1], safety PK/PD on gastric pH	 PK[1] PK/PD on gastric pH

[1]Extrapolation

Esomeprazole (Nexium): Similar Exposure-Response on gastric pH supported the extrapolation and the dosing in infants





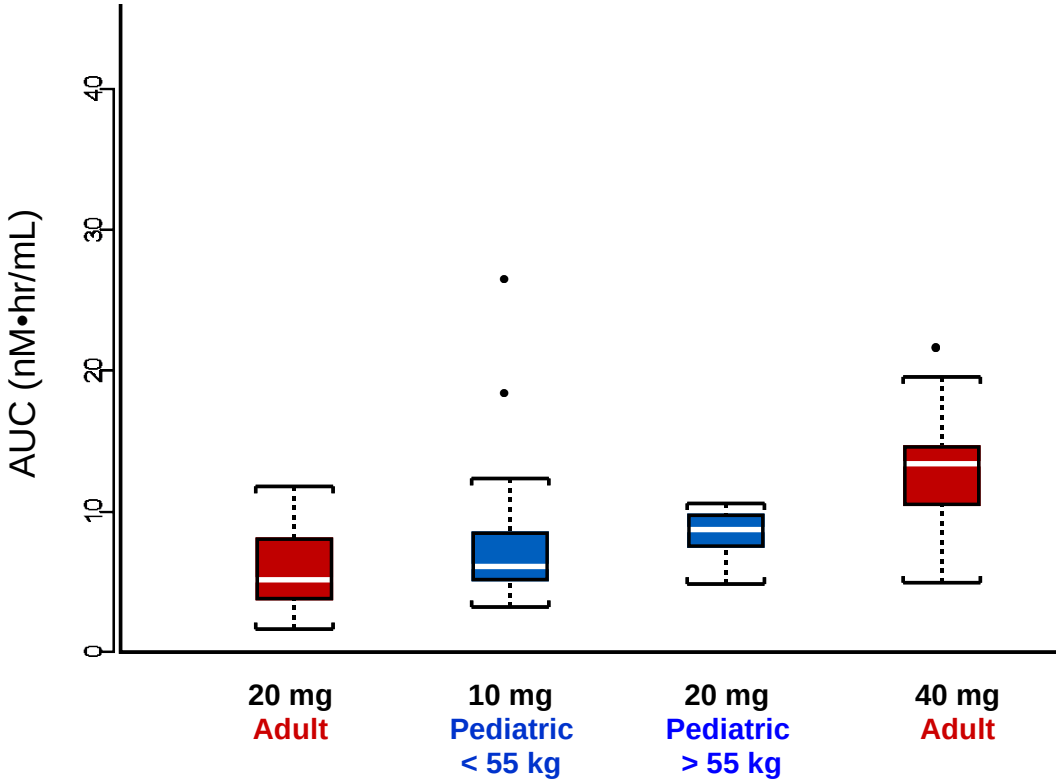
PK Guided Dose Selection: IV Nexium®

- Treatment of GERD with EE
  - Adult dose: 20 mg and 40 mg

- Pediatric Nexium IV

– Full extrapolation
– Pop PK & Safety Data: 50 pediatrics (0 – 17 yr)
– Dosing regimen adjusted so AUC and Cmax values match adult data at 20 mg

Nexium IV:
AUCs Values in Pediatrics* ~ Adults

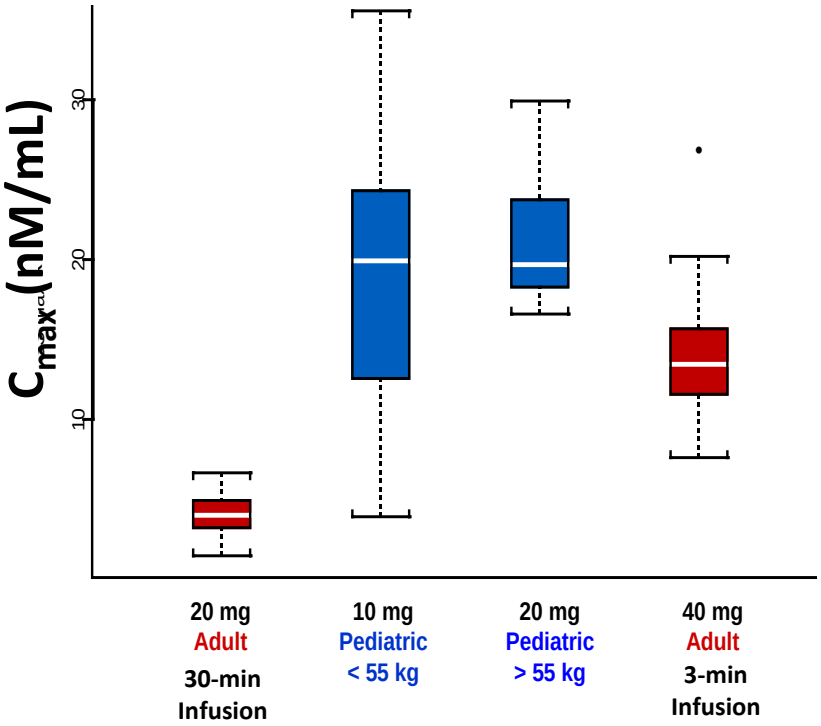


NDA 21-689/S-017 Clinical Pharmacology Review by Dr. Earp

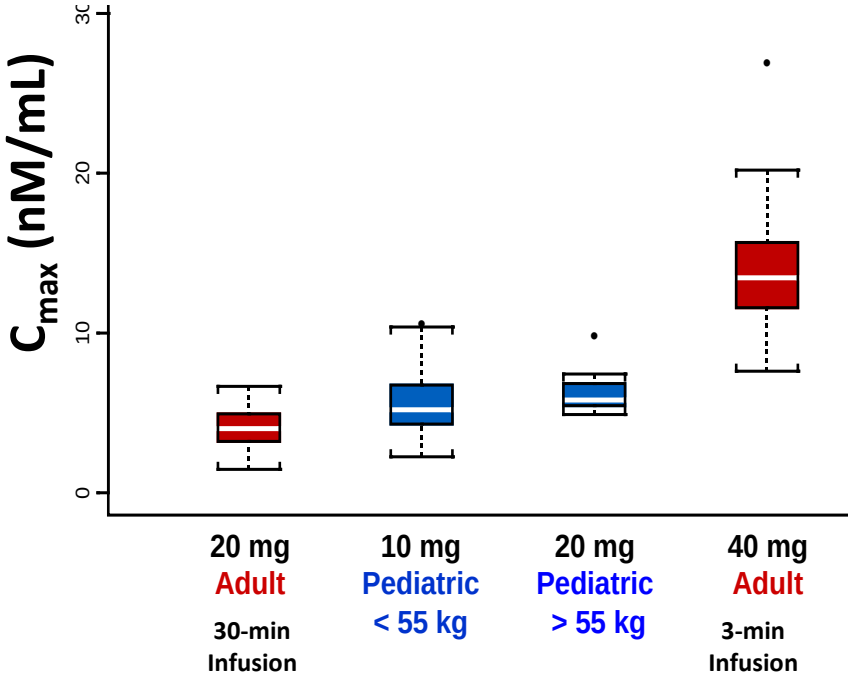
*** 1-17 years old**

Adjustment of the infusion duration for Cmax

For 3 min Infusion



For 30 min Infusion*



10-min infusion: C_{max} < 40 mg in adults (13.5 nM/mL)

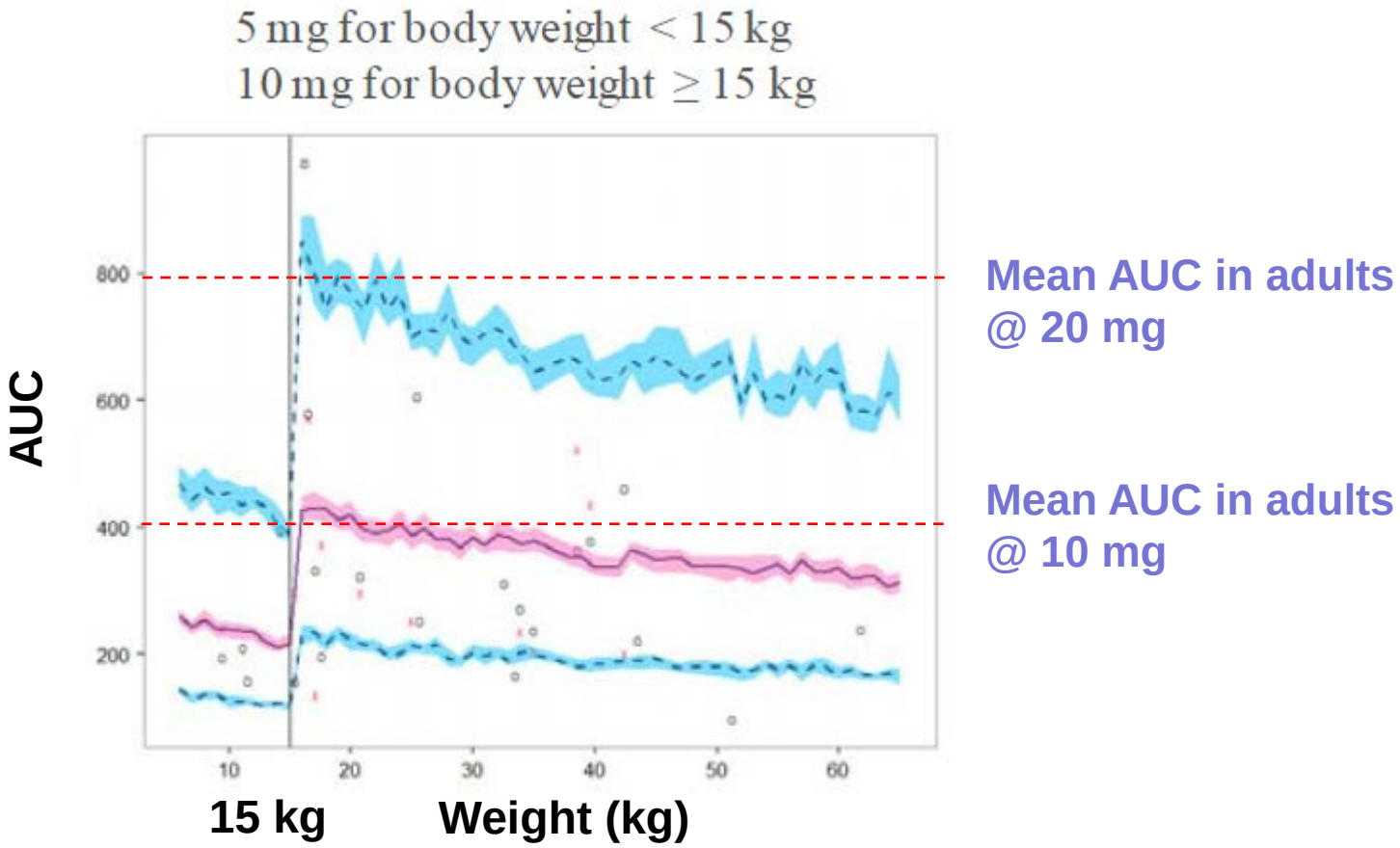
*** Simulated**

AcipHex®: Dose selection for patients 1-11 years old

- Dose for patients 1-11 years old
  - < 15 kg: 5 mg QD with the option to increase to 10 mg QD
  - ≥ 15 kg: 10 mg QD
- Pediatric systemic exposures at 10 mg
  - Lower than those at 20 mg in adults
  - Comparable to those at 10 mg in adults
- Healing of EE was evident in patients 1-11 years old
  - Healing rate was comparable to adult healing rate at 10 mg

Lower exposure in pediatric patients

Predicted median AUCs (pink) and 95% CI (blue)



Sponsor's population PK analysis; NDA 204-736 Clinical Pharmacology Review

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204736Orig1s000ClinPharmR.pdf

Effectiveness on healing of EE in patients 1-11 years of age supported the dosing

1-11 year-old

Endoscopic Classification of GERD At Baseline	Healing Rate at 12 weeks		
	Body Weight <15 kg		Body Weight ≥15 kg
	5 mg dose	10 mg dose	10 mg dose
Erosive[a]	88% (7/8)	83% (5/6)	71% (12/17)
Non-erosive[b]	78% (7/9)	100% (10/10)	81% (17/21)

[a]Hetzel-Dent score ≥2
[b]Hetzel-Dent score = 1

Adults

HEALING OF EROSIVE OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD)
PERCENTAGE OF PATIENTS HEALED

Week	10 mg ACIPHEX QD N=27	20 mg ACIPHEX QD N=25	40 mg ACIPHEX QD N=26	Placebo N=25
4	63%*	56%*	54%*	0%
8	93%*	84%*	85%*	12%

*(p<0.001 versus placebo)

No apparent D-R relationship in adults

Case Summary

- Similar E-R relationship on gastric pH supported the extrapolation of efficacy and the dosing for EE in infants, 1-11 months old

- Dose selection based on Cmax and AUC matching to the range of Cmax and AUC observed in adults
  - Dosing based on body-weight cut-off to reduce the PK variability across age groups
  - Modeling and simulation to refine the dosing regimen

- With the exposure-matching approach, the identification of the optimal dose in pediatric patients is dependent on the finding of optimal dose in adults

Acknowledgements

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