Extrapolation of Adult Efficacy Data to Pediatric Patients

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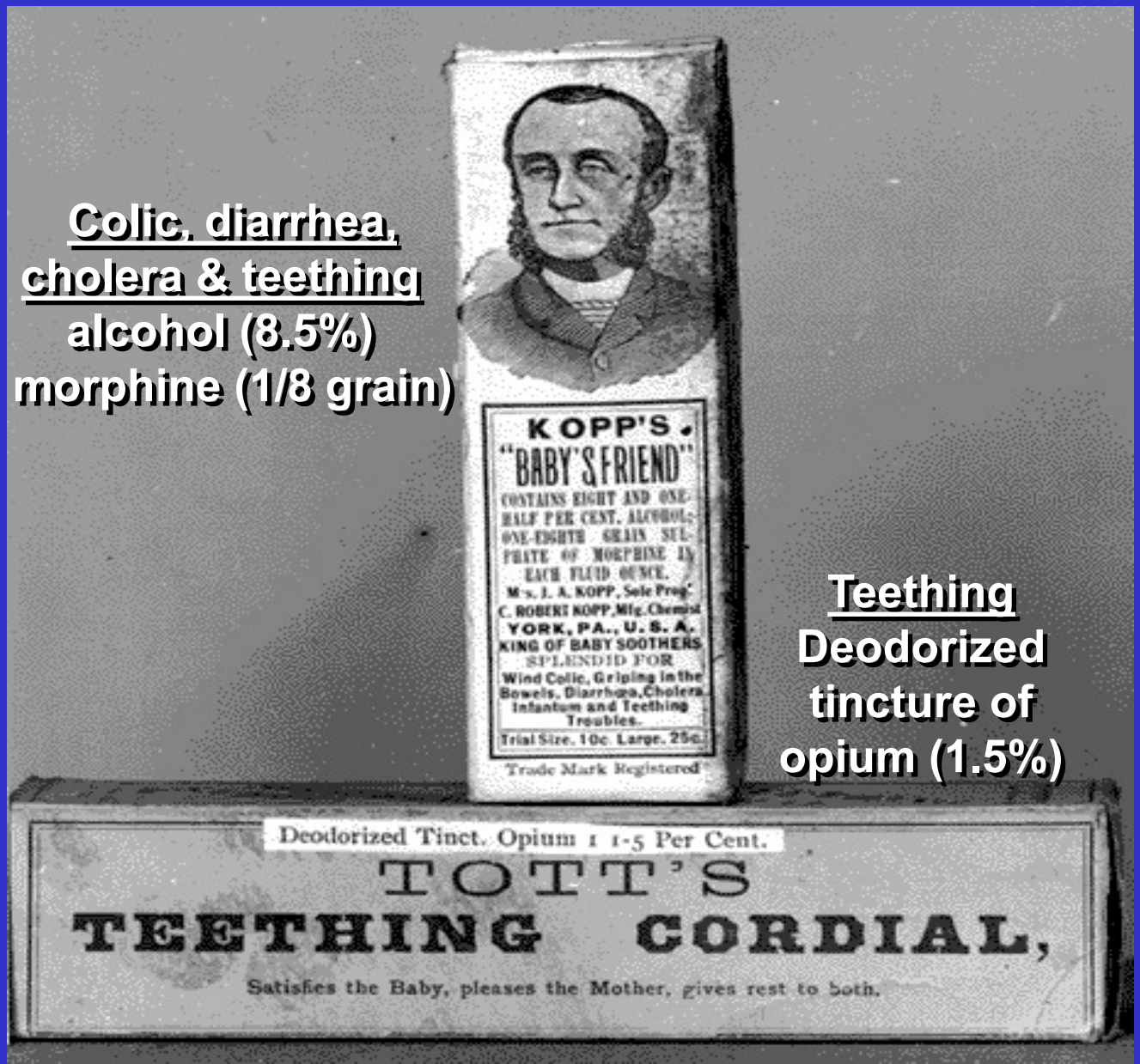
Disclosure(s)

- No conflicts to disclose
- Off label drug use in neonates, treated in NICUs, is the current standard and therefore will be presented

Historical Drug "Development" in Children



Medication Use in NICUs – Pediatrix, Inc. Data for 2007: 72,647 Patients - Rate/1000 Discharges

Drug	Rank	Use
Gentamicin	1	822
Ampicillin	2	726
Surfactants	3	234
Caffeine	4	224
Furosemide	5	199
Vancomycin	6	177
Metoclopramide	7	82
Fentanyl	8	95
Dopamine	9	89
Midazolam	10	80
Morphine	11	71
Ranitidine	12	70
Cefotaxime	13	62
Phenobarbital	14	59
Indomethacin	15	54

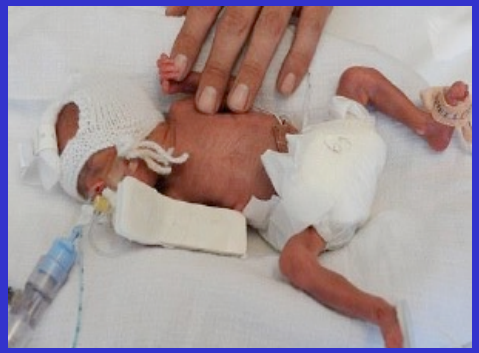
Data from Reese Clark 2007

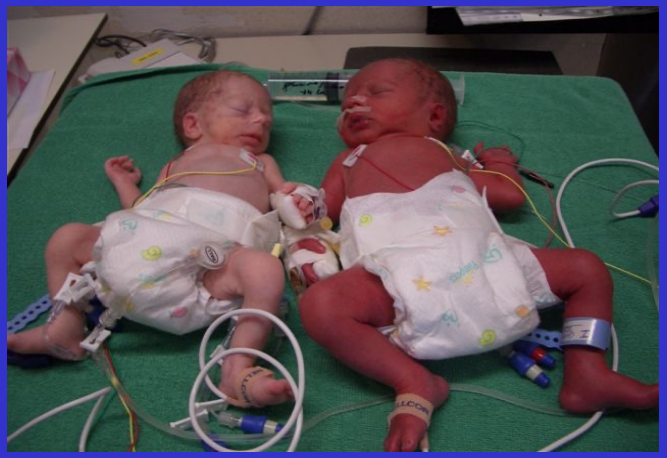
Medication Use in NICUs, 2014

Drug	Rank	
Ampicillin	1	
Gentamicin	2	
Caffeine	3	
Vancomycin	4	
Beractant	5	
Furosemide	6	
Fentanyl	7	
Dopamine	8	
Midazolam	9	
Calfactant	10	
Metoclopramide	11	
Ranitidine	12	
Poractant alpha	13	
Morphine	14	
Cefotaxime	15	

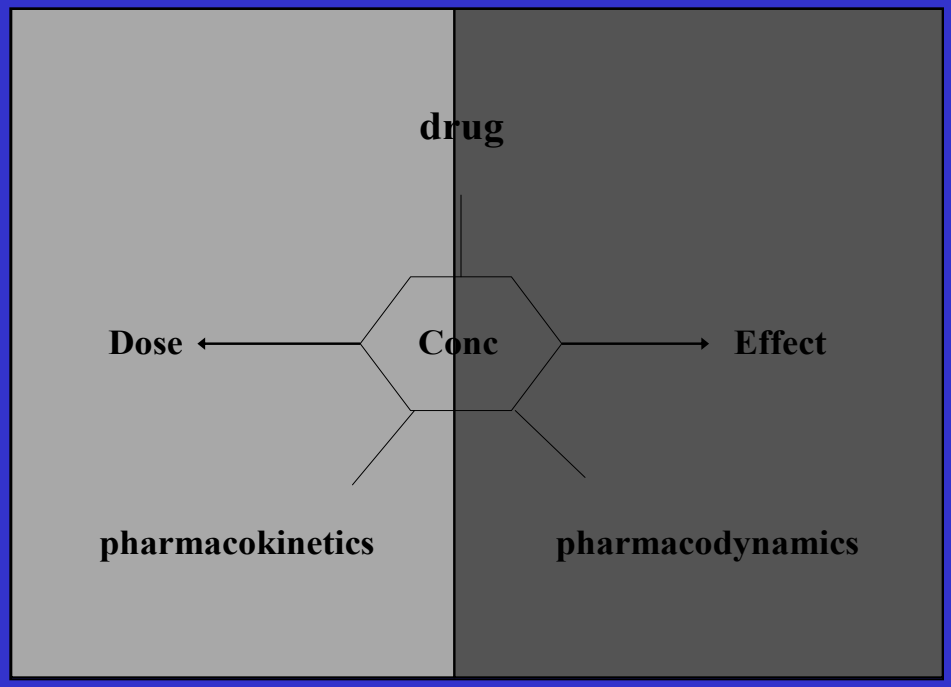
Data from PTN network 2014

Neonatal Clinical Pharmacology





Role of Clinical Pharmacology



PK : what the body does to the drug: conc/time
PD: what the drug does to the body : conc/effect

Extrapolation of Adult Efficacy Data to Pediatric Patients

Given the available data, is there a biological reason to believe that drugs with a well-established MOA (opioids, NSAIDs, acetaminophen, and local anesthetics) would be less effective (at similar concentrations) in pediatric patients less than 2 years of age compared to older children? If so, in which age group and what are the uncertainties? Assessment of PK and safety would be required in all age groups.

The FDA Extrapolation Decision Tree

When Compared to Adults, Is Disease Progression and Response to Intervention Similar in Pediatrics?

Answer : No

The FDA Extrapolation Decision Tree

NO EXTRAPOLATION

CONDUCT

1) Adequate dose-ranging studies in children to establish dosing
2) Safety and efficacy trials at identified dose(s)

The FDA Extrapolation Decision Tree

Similar Exposure-Response in Pediatrics and Adults?

Answer : Yes

The FDA Extrapolation Decision Tree

Is the Drug (or active metabolite) Concentration Measurable and Predictive of Clinical Response?

Answer : Yes

The FDA Extrapolation Decision Tree

FULL EXTRAPOLATION

CONDUCT

1) Adequate PK study to select dose(s) to achieve similar exposure in adults
2) Safety trials at identified dose(s)

The FDA Extrapolation Decision Tree

Similar Exposure-Response in Pediatrics and Adults?

Is the Drug (or active metabolite) Concentration Measurable and Predictive of Clinical Response?

Answers : No

The FDA Extrapolation Decision Tree

Is There a PD Measurement That Can be Used to Predict Efficacy in Children?

Answer: Yes or No

The FDA Extrapolation Decision Tree

PARTIAL EXTRAPOLATION

CONDUCT

1) Adequate dose-ranging studies in children to establish dosing
2) Safety and efficacy/PD trials at identified dose(s)

Extrapolation of Adult Efficacy Data to Pediatric Patients

Given the available data, is there a biological reason to believe that drugs with a well-established MOA (opioids, NSAIDs, acetaminophen, and local anesthetics) would be less effective (at similar concentrations) in pediatric patients less than 2 years of age compared to older children? If so, in which age group and what are the uncertainties? Assessment of PK and safety would be required in all age groups.