

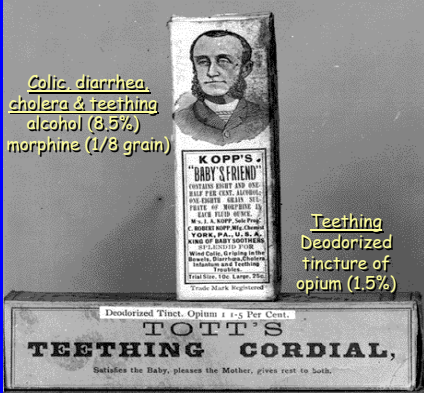
Developmental and Pediatric Pharmacology

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February 18, 2010

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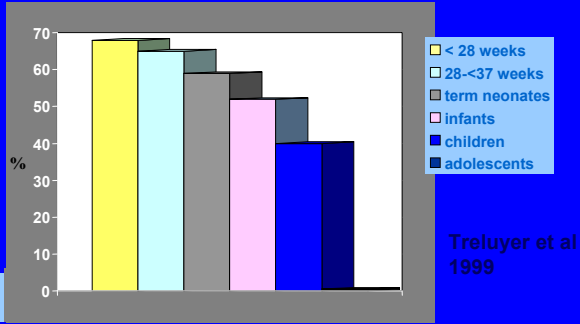
Colic, diarrhea,
cholera & teething
alcohol (8.5%)
morphine (1/8 grain)



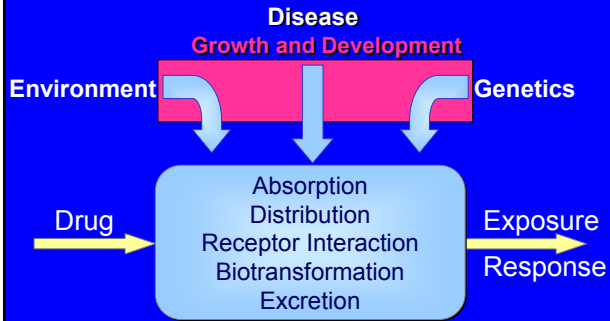
Teething
Deodorized
tincture of
opium (1.5%)



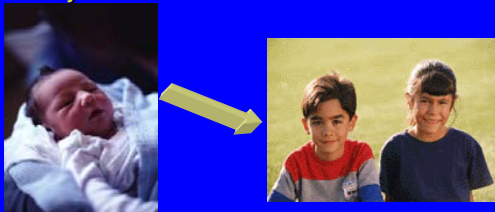
Unlicensed and « off-label drugs » in paediatric and neonatal intensive care units



Determinants of Drug Response in Infants



The Challenge of Pediatric Clinical Pharmacology: Determining the Source(s) of Variability.....



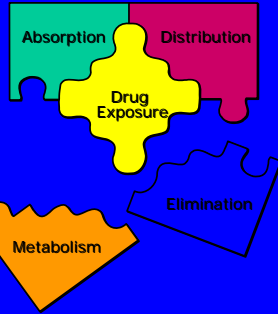
Ontogeny

Pharmacogenetics

Variability

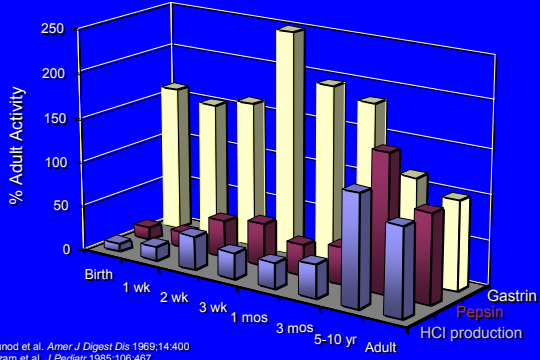
Critical Role of Pharmacokinetics in Pharmacotherapy.....

- The combination of **ADME** dictate exposure which dictates dose.



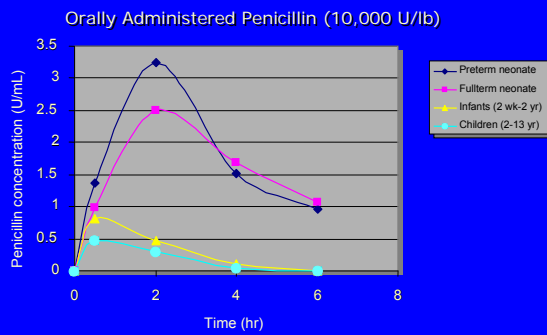
- Exposure along with the interaction with therapeutic targets (e.g., receptors) dictates response.

Drug Absorption Developmental Changes in Gastric pH



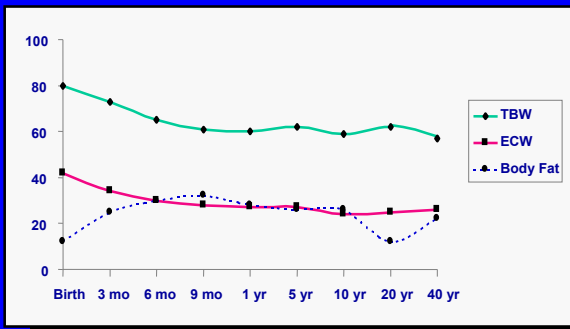
Agunod et al. *Amer J Digest Dis* 1969;14:400
 Mozam et al. *J Pediatr* 1985;106:467
 Rodgers et al. *J. Pediatr Surg* 1976;13:13

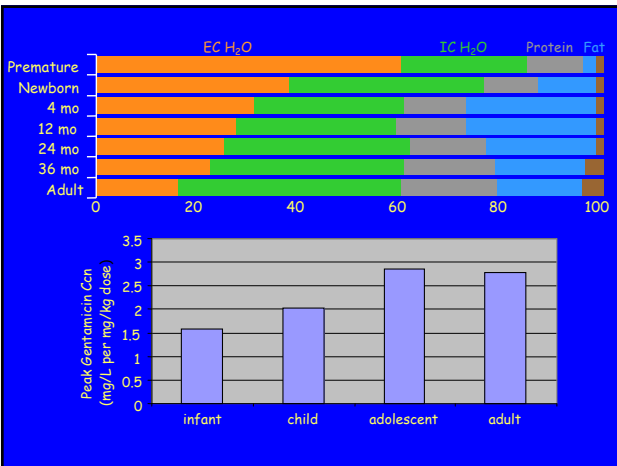
Developmental Alterations in Intestinal Drug Absorption Influence of Higher Gastric pH



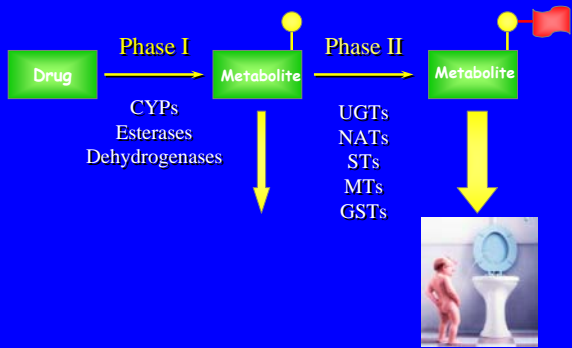
Huang et al. *J Pediatr* 1953;42:657

Drug distribution Age-dependent changes in body composition



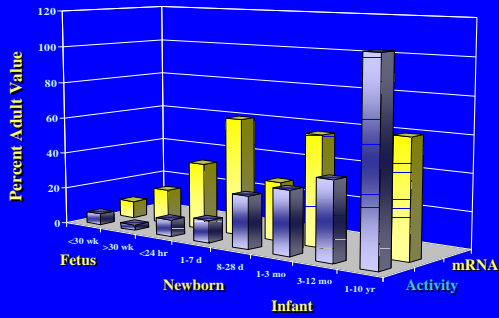


Drug Biotransformation



Ontogeny of CYP3A4

From Lacroix D et al. *Eur. J. Biochem.* 247: 625-634, 1997

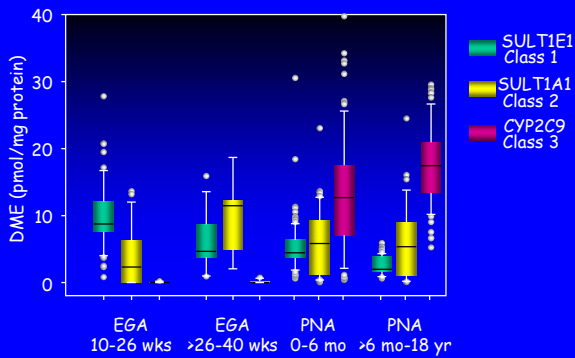


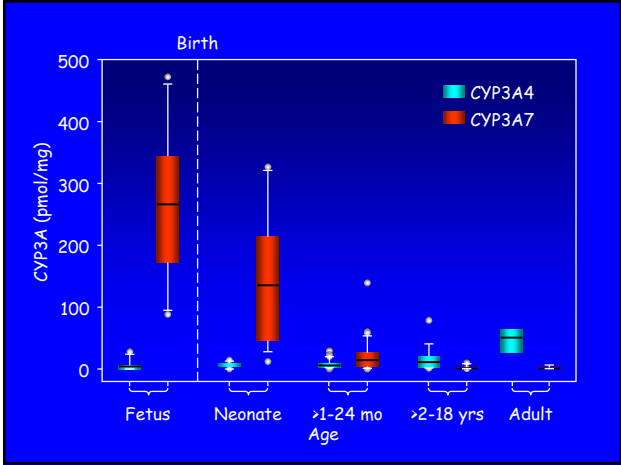
Human Hepatic DME Ontogeny

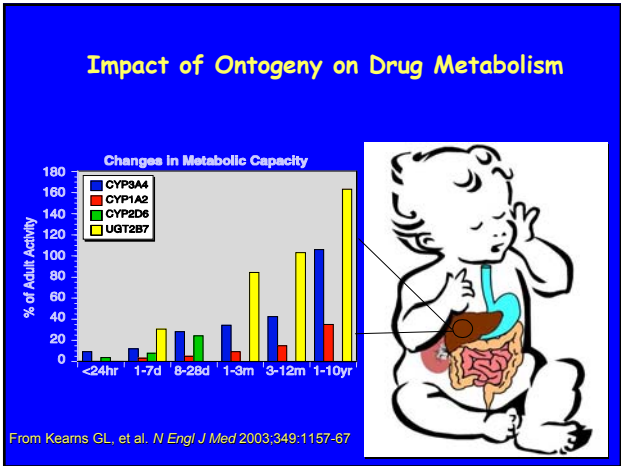
Class 1	Class 2	Class 3	
ADH1A	CYP2C19	ADH1B	EPHX2
CYP3A7	CYP3A5	ADH1C	FMO3
FMO1	GSTA1	AOX	GSTM
GSTP	GSTA2	CYP1A2	SULT2A1
SULT1E1	SULT1A1	CYP2C9	UGT1A1
SULT1A3		CYP2D6	UGT1A6
		CYP2E1	UGT2B7
		CYP3A4	PON1
		EPHX1	

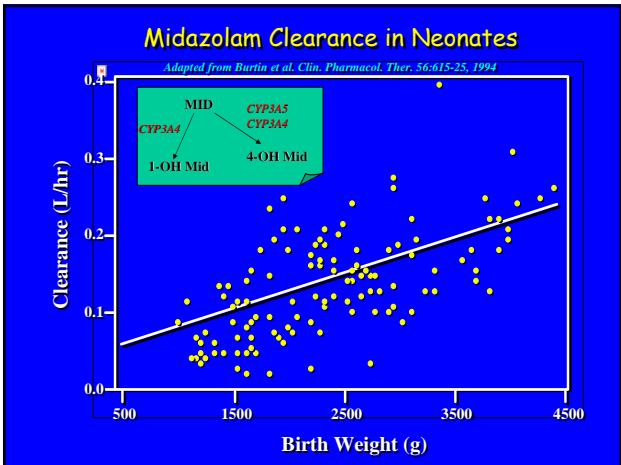
Hines, *Pharmacol & Therap.* 118:250-267, 2008

Human DME Ontogeny







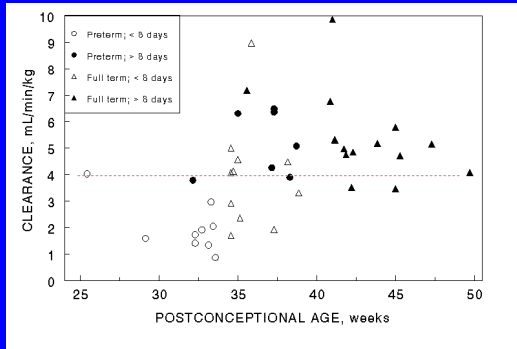


Impact of Age on Linezolid Pharmacokinetics

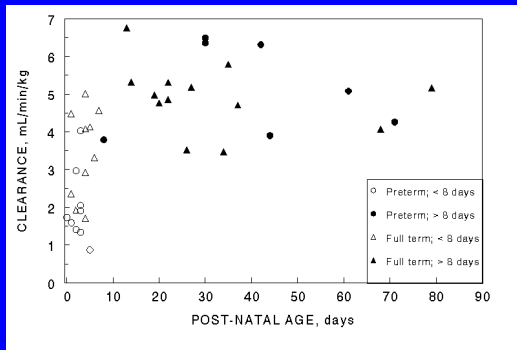
Kearns GL, Jungbluth GL, Abdel-Rahman SM, Hopkins NK, Welshman IR, Grzebyk RP, Bruss JB, van den Anker JN. Impact of ontogeny on linezolid disposition in neonates and infants. *Clin Pharmacol Ther* 2003;74(5):413-422.

Parameter	Adult (n=57)	Child (n=44)	Infant (n=10)
Vdss (L/kg)	0.63 ± 0.13	0.71 ± 0.18	0.83 ± 0.18
Cl (L/hr/kg)	0.10 ± 0.03	0.30 ± 0.12	0.52 ± 0.15
t _{1/2} (hr)	4.6 ± 1.7	3.3 ± 0.9	2.0 ± 0.9
C _{max} _{norm} (mg/L)	19.7 ± 4.9	17.0 ± 5.2	12.5 ± 3.5
C _{12 pred} (mg/L)	3.3 ± 2.1	0.41 ± 0.72	0.03 ± 0.05
T > MIC ₉₀ (%)	70-100%	35-70%	20-35%

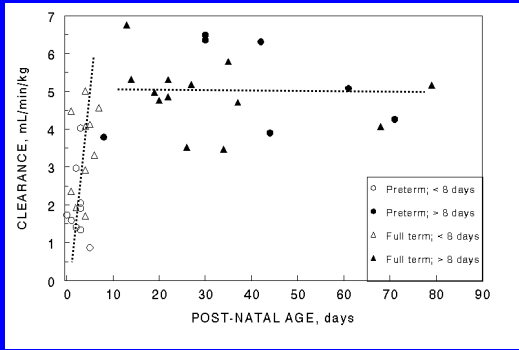
Linezolid Plasma Clearance Association with PCA



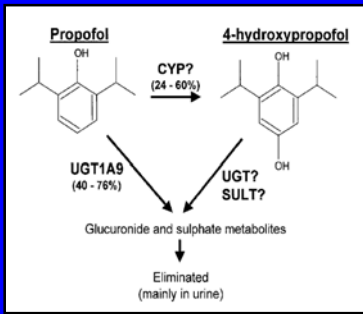
Linezolid Plasma Clearance Association with PNA

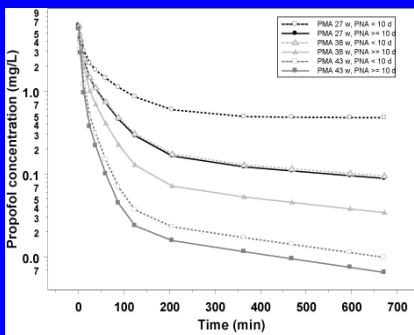


Linezolid plasma clearance in neonates

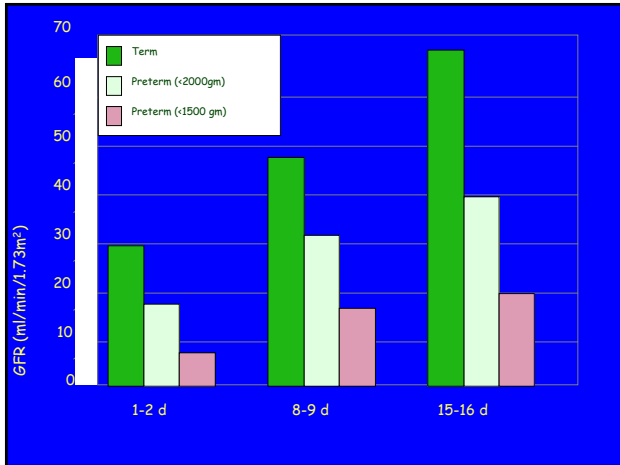


Propofol clearance almost exclusively depends on metabolic clearance





Allegaert K, et al. Inter-individual variability in propofol pharmacokinetics in preterm and term infants. Br J Anesth 2007 dec 99(6):864-70.



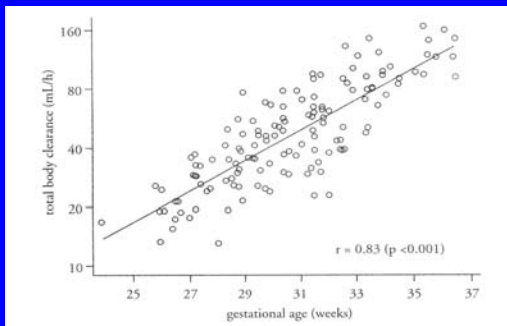
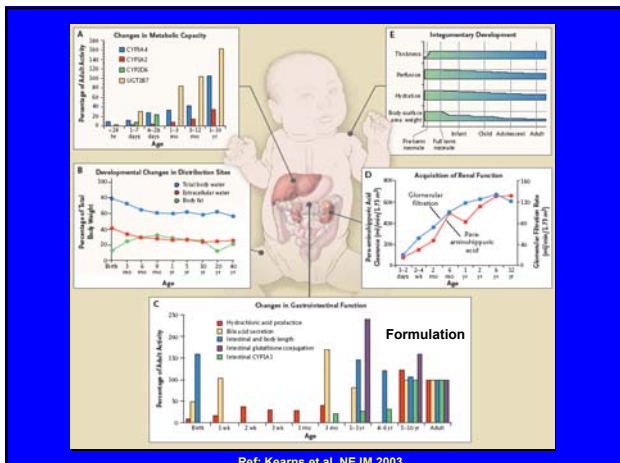


Figure 1. Linear regression analysis of total body clearance of ceftazidime (mL/h) versus gestational age (weeks) in 136 preterm infants on day 3 after birth. Note the logarithmically transformed vertical axis



Ref: Kearns et al, NEJM 2003

All neonates are not created equal

- post-conceptual age
- gestational age
- postnatal age
- asphyxia at birth
- PDA
- prenatal drug exposure

These will increase variability in outcome measures

Factors influencing drug disposition in infants, children and adolescents.....



- Genetics
- Environment
- Disease
- Treatment
- Growth and development

Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus

Objective: Our objective was to study the pharmacokinetics of ibuprofen in preterm infants with patent ductus arteriosus on day 3 and day 8 after birth.

Methods: Ibuprofen was administered on days 3, 6, and 8 by a 15-minute intravenous infusion of 10, 6, and 3 mg/kg, respectively, with the aim of closing the ductus arteriosus. Blood samples were drawn at time zero and at 0.5, 1, 2, 4, 8, 16, and 24 hours after the first and third doses. Ibuprofen plasma concentrations were assayed by HPLC.

Results: A total of 27 preterm infants were included (gestational age, 28.6 ± 1.9 weeks; birth weight, 1200 ± 400 g; values are mean ± standard deviation). Ibuprofen pharmacokinetics followed a 2-compartment open model. Between the first and third doses (day 3 and day 8) there was a significant decrease of the values of distribution of the central compartment (V_d), (18.2 ± 4 versus 9.17 ± 1.9 L/kg, $P = .03$) and area under the plasma concentration-time curve (524 versus 447 mg · h/L, $P = .03$). The decrease in V_d was more pronounced in patients with a closing ductus. Total body clearance and plasma half-life did not change significantly. No significant differences were observed in ibuprofen peak plasma concentrations after the first and third doses in relation to ductus status after treatment.

Conclusion: Ibuprofen pharmacokinetics showed a large interindividual variation in preterm infants during treatment for patent ductus arteriosus, and significant changes may occur between day 3 and day 8 after birth in these infants with a closing ductus. These findings may have implications for the treatment selected with ibuprofen in patients with patent ductus arteriosus. (Clin Pharmacol Ther 2001;70:556-63.)

Bart Van Overbeek, MD, PhD, Duan Tsoo, PharmD, PhD, Paul J. C. Schepers, PhD, Gregory L. Kearns, PharmD, and John N. van den Anker, MD, PhD
Edgewood Hospital, Belgium, Amsterdam and Rotterdam, The Netherlands, Kansas City, Mo, and Columbus, Ohio

Elevated Morphine Concentrations in Neonates Treated With Morphine and Prolonged Hypothermia for Hypoxic Ischemic Encephalopathy

Anikó Róka, MD*, Kis Tamas Melinda, MD*, Barna Vicsárihelyi, PhD*, Tamás Machay, PhD*, Denis Azzopardi, MD*, Miklós Szabó, PhD*

*First Department of Paediatrics, Semmelweis University, Budapest, Hungary; †Research Group of Paediatrics and Nephrology, Hungarian Academy of Sciences, Budapest, Hungary; ‡Division of Clinical Sciences, Hammersmith Campus, Imperial College London, United Kingdom

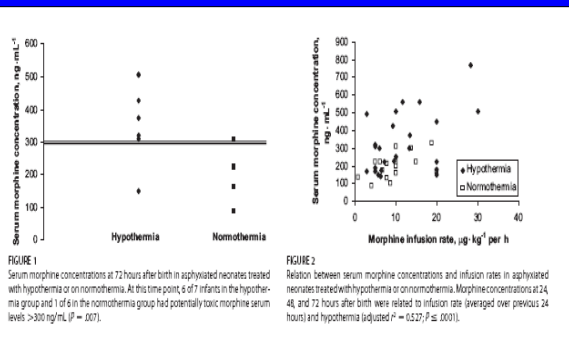
The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Data obtained in adults indicate that even short-term hypothermia may have an effect on the metabolism of major analgesics and other drugs. No data are available for neonates concerning the impact of hypothermia on the pharmacokinetics of morphine.

What This Study Adds

The aim of our observational study, therefore, was to investigate whether morphine pharmacokinetics are altered during prolonged moderate systemic hypothermia in asphyxiated neonates, resulting in excessively high morphine concentrations compared with infants kept at normothermia; this would be important information for clinicians wishing to provide hypothermia.



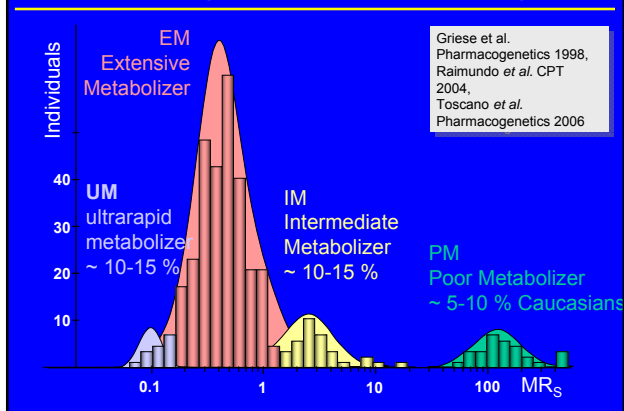
PHARMACOGENETICS

The study of the role of genetic factors in drug disposition, response and toxicity - relating variation in human genes to variation in drug responses at the level of the individual patient (the right drug for the right patient)

CYP2D6 Pharmacogenetics

- ❖ CYP2D6 activity displays bimodal distribution in Caucasian subjects
- ❖ 5-10% of Caucasian population deficient in CYP2D6 activity
- ❖ “Poor metabolizers” or “PMs” have two “inactive” forms (alleles) of the CYP2D6 gene
- ❖ PMs at increased risk for concentration-dependent side effects with “normal” drug doses
- ❖ Some drugs may not work (codeine; tramadol)

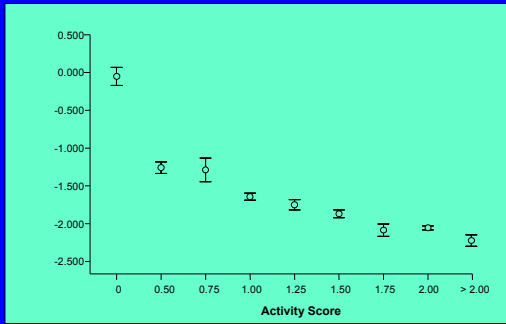
Unravelling CYP2D6 Pharmacogenetics



Inferring CYP2D6 Phenotype from Genotype: “Activity Score”

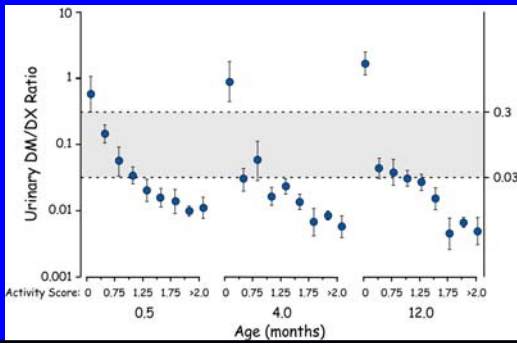
2	*1x2, *2x2
1	*1, *2, *10x2, *35, *41[2988G]
0.75	*9, *29, *45, *46
0.5	*10, *17, *41[2988A]
0	*3, *4, *5, *6, *7, *8, *11, *12, *15, *36, *40, *42

Relationship between CYP2D6 activity (DM/DX) and Activity Score

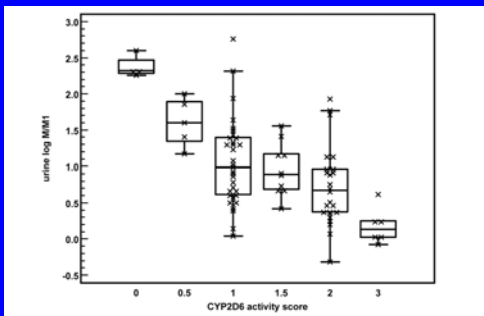


Blake M. et al. 2007

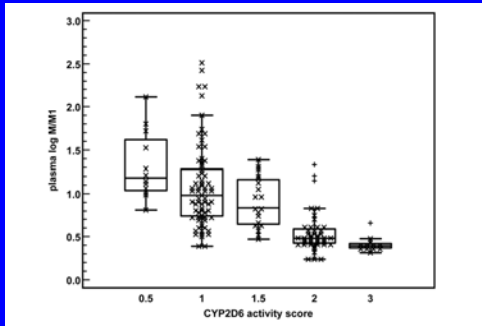
CYP2D6 Genotype-Phenotype Correlation in First Year of Life



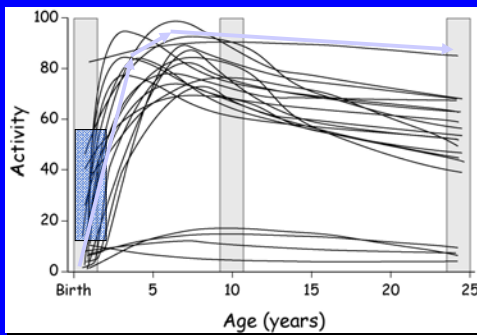
Postmenstrual Age and CYP2D6 Polymorphisms Determine Tramadol O-Demethylation in Critically ill Neonates and Infants (Allegraert K, van den Anker JN, et al. *Pediatr Res*, 2008)



Postmenstrual Age and CYP2D6 Polymorphisms Determine Tramadol O-Demethylation in Critically ill Neonates and Infants (Allegaert K, van den Anker JN, et al. Pediatr Res, 2008)



Developmental Trajectories: Pediatric Pharmacogenetics





Case Report

Lancet 2006; 368: 704

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Goodijk, Steven J. Leader

- full-term healthy male infant
- day 7 pp: intermittent periods of difficulty in breastfeeding
- day 11: the baby had regained his birthweight
- day 12: grey skin, milk intake had fallen
- day 13: the baby was found dead

- autopsy: no abnormality
- blood concentration of morphine (metabolite of codeine): **70 ng/mL versus 0-2.2 ng/mL (typical)**

Pharmacogenetics of Codeine

codeine

site of action

Cytochrome P450 2D6

morphine

Blood brain barrier

plasma morphine levels after 170 mg codeine p.o.

Time [h]	Poor Metabolizer (µmol/L)	Extensive Metabolizer (µmol/L)
0	0	0
1	~55	~15
2	~45	~10
4	~35	~5
6	~25	~2
8	~15	~1
10	~10	~0.5
15	~5	~0.2
20	~2	~0.1
25	~1	~0.05

Eckhardt et al., Pain 199

Case Report

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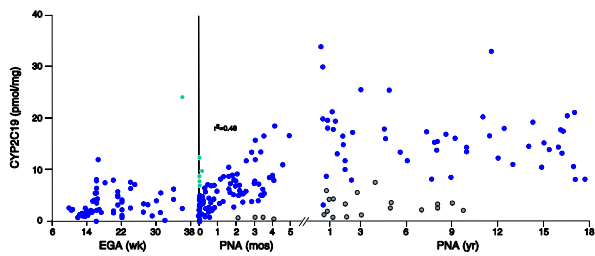
Explanation:

- medication mother due to episiotomy pain: codeine 60 mg plus paracetamol 1000 mg every 12 hrs for 2 weeks
- Morphine concentration in stored milk: 87 ng/mL
- mother: CYP2D6 genotype: *CYP2D6**2x2 gene duplication = **Ultra rapid metabolizer phenotype**

CYP2C19 Pharmacogenetics

- 1984: Unusual sedation in a subject receiving anticonvulsant mephenytoin
- Impaired 4-hydroxylation of S-mephenytoin
- Affects 2-5% of Caucasians; 20-25% of Asians
- Affected drugs include omeprazole, lansoprazole, pantoprazole, diazepam
- Major clinical consequence at present related to omeprazole pharmacodynamics and efficacy

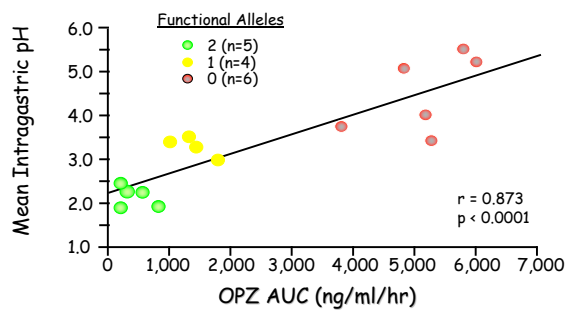
Developmental Alterations in CYP2C19 Expression



Koukouritaki et al. *J Pharmacol Exp Ther* 2004;308:965

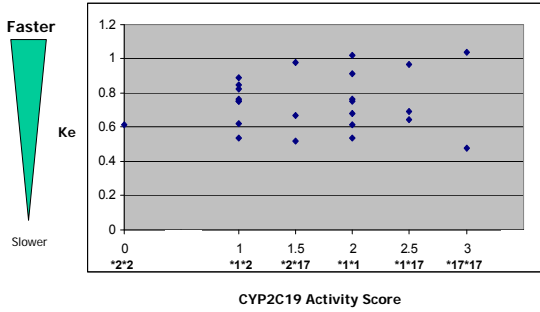
CYP2C19 Pharmacogenetics

Omeprazole PK After a Single 20 mg Oral Dose

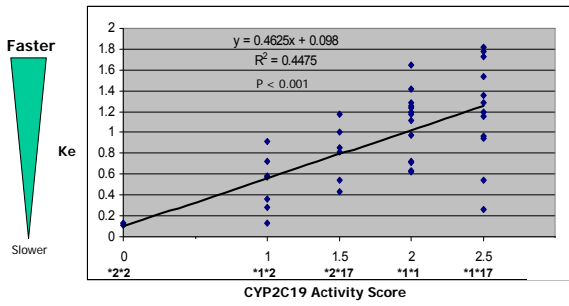


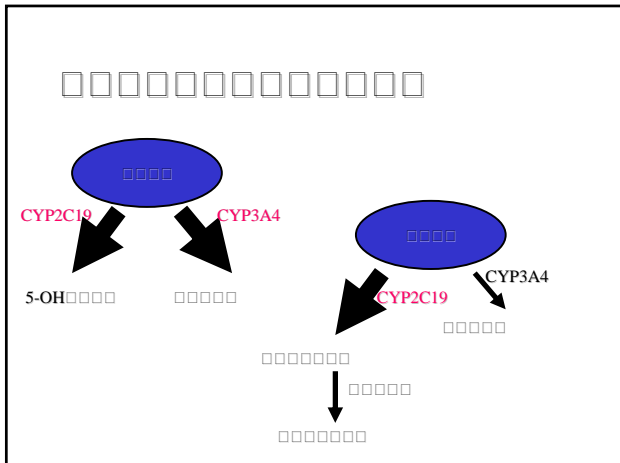
Sagar M, et al. *Gastroenterology* 2000;119:670-676

Drug X: no relationship between CYP2C19 activity score and Clearance

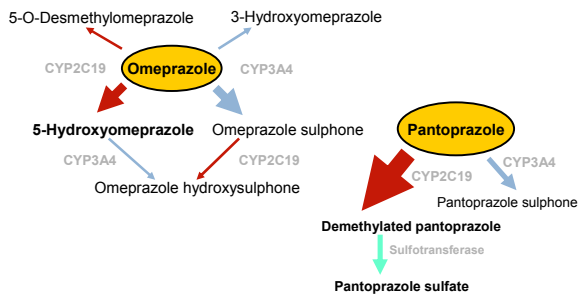


Drug Y: a clear relationship between CYP2C19 activity score and Clearance





Metabolic Pathways for Selected Proton Pump Inhibitors



The need for drug studies in critically ill preterm infants

- Drug studies in adults or animal models may not adequately predict pharmacokinetic or pharmacodynamic properties in neonatal patients
- Unable to reliably extrapolate adult data to the neonatal population
- Drugs must be studied in neonates to determine their pharmacokinetics, pharmacodynamics, appropriate dose, safety and efficacy



