NEONATAL PHARMACOLOGY

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OBJECTIVES

- Describe medication use in neonates and mothers (pre and postnatal)
- Identify characteristics of maternal drugs that may impact fetus/neonate
- Define the impact of pharmacokinetics on neonatal drug exposure
- Review examples of medication use in neonates where neonatal pharmacology is important

DRUG THERAPY

- Goal is to administer a given drug at a given dose to achieve a desired therapeutic effect while minimizing risk of toxicity

Pauwels S, Allegaert K. Arch Dis Child 2016;0:1–5.

MEDICATION USE IN NEONATES

- Nearly all medications used in the NICU are done so off-label
- Limited clinical data in neonates leads to extrapolation from more extensively studied patient populations
  - Clinical data from other patient populations with animal data and known developmental pharmacology of neonates to determine best guess for drug and dosing regimens
- Maturation of organ systems leads to differences in dosing needs throughout spectrum of NICU stay
  - Up to 1-log value of variability seen intra- and interpatient weights (0.5 to 5 kg)

HISTORY OF UNEXPECTED ADVERSE EFFECTS

- Kernicterus (sulfonamides, ceftriaxone, ibuprofen?)
- Gray baby syndrome (chloramphenicol)
- Gasping syndrome (benzyl alcohol—enoxaparin, midazolam)
- Apnea (promethazine)
- Metabolic acidosis (propylene glycol)

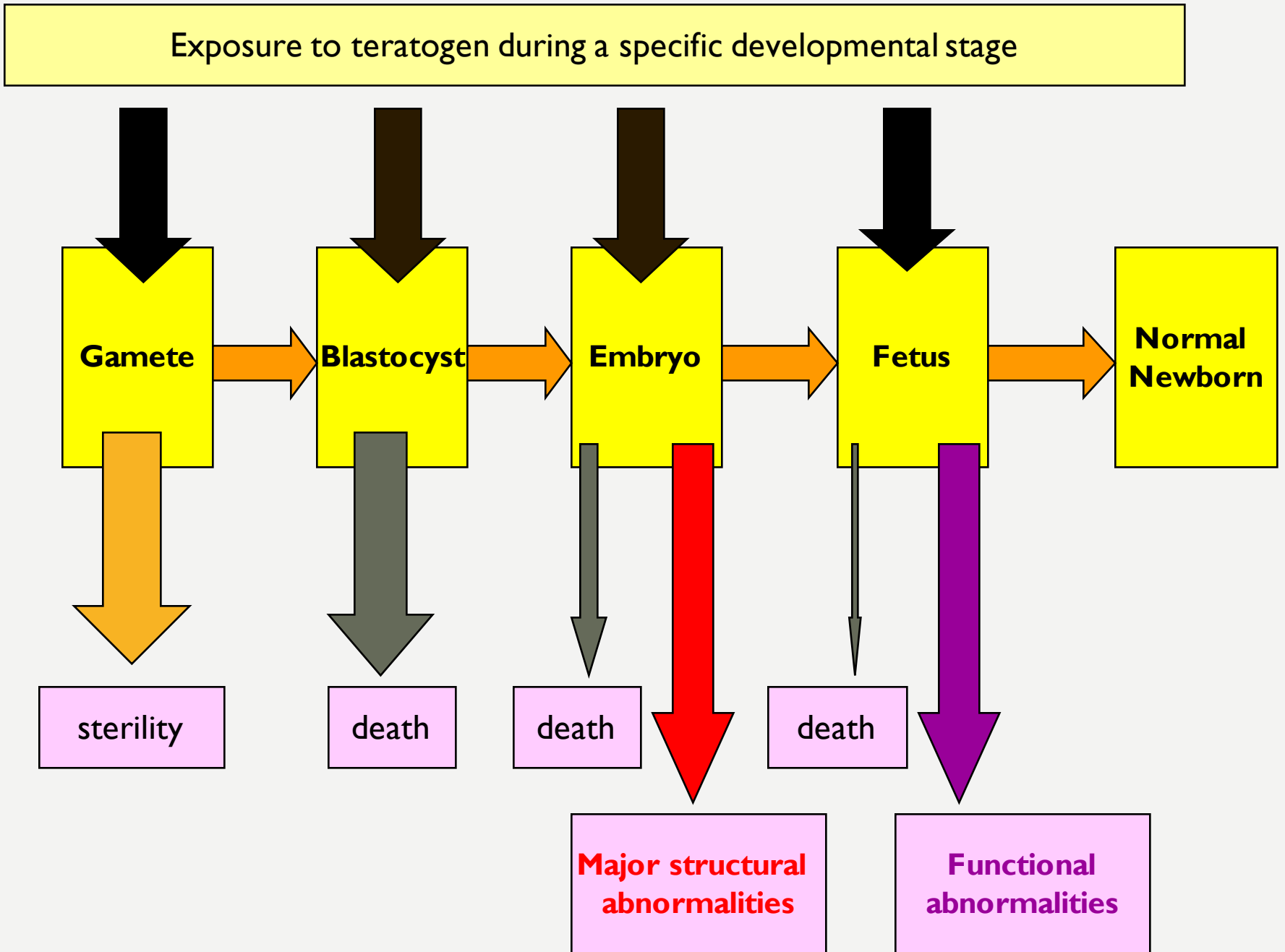
NEONATAL PHARMACOLOGY

- Prediction of drug-specific effects and adverse effects based on pharmacokinetics and pharmacodynamics
  - Pharmacokinetics: concentration/time profile
  - Pharmacodynamics: concentration/effect profile

MATERNAL DRUG EXPOSURE

- More than 90% of pregnant women self-report taking at least one medication during pregnancy[1]
  - Average number of medications: 4.2
  - Half of all pregnant women take more than 4 medications

1. Koren et al. JPPT 2013


Exposure to teratogen during a specific developmental stage
Gamete
Blastocyst
Embryo
Fetus
Normal Newborn
sterility
death
death
death
Major structural abnormalities
Functional abnormalities

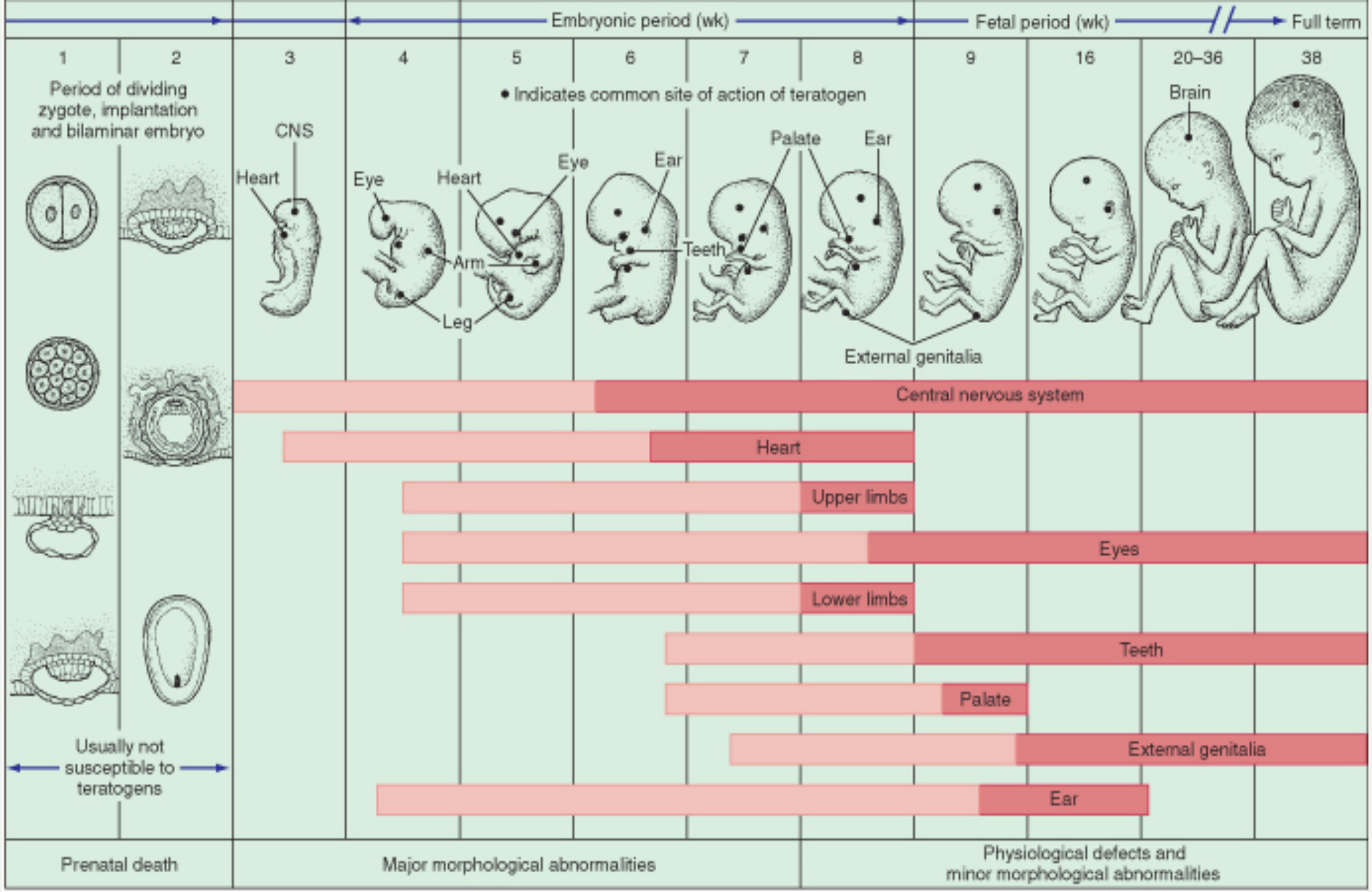


Figure 6-8 Schematic illustration of the sensitive or critical periods in prenatal development. *Dark boxes* denote highly sensitive periods; *light boxes* indicate states that are less sensitive to teratogens. (From Moore KL: *Before We Are Born: Basic Embryology and Birth Defects*, 2nd ed. Philadelphia, WB Saunders, 1977.)

DRUG TRANSFER ACROSS THE PLACENTA

- Most drugs ingested by pregnant women cross the placenta
  - Most women expose fetus to 1-8 drugs during pregnancy
- Human placenta unique from other species as organ of drug transfer
  - Higher permeability after16 weeks gestation
  - Later in gestation, increases in uterine blood flow→ higher passage across the placenta

DRUG TRANSFER ACROSS THE PLACENTA

- Most drugs cross via passive diffusion
- Characteristics of highly diffused drugs:
  - Low molecular weight ($\leq$ 600 d), non-ionized, lipid soluble
- Strongly ionized compounds poorly diffuse
  - Exceptions: ampicillin, methicillin

DRUG TRANSPORT ACROSS THE PLACENTA

- Facilitated diffusion: concentration gradient, requires no energy, inhibited by competitive analogues, saturable
- Occurs with drugs structurally similar to endogenous compounds
  - Cephalosporins, gancyclovir, and corticosterone

PLACENTAL PROTECTION FOR FETUS

- Placental function
  - Semipermeable barrier
  - Limited drug metabolism by placenta
- Drugs enter the fetus through the umbilical vein
  - 40-60% of the umbilical blood flow enter into the fetal liver

FDA PREGNANCY CATEGORIES

Category	Animal Data	Human Data
A	No risk	No risk
B	No risk	No data
	Risk	No risk
C*	Risk	No data
D*	Harmful	Harmful
X	Harmful	Harmful

*Potential benefit may outweigh potential risk to fetus

FDA PROPOSED CHANGES TO LABELING

- Elimination of the 5 categories
  - Misleading to providers and women
  - Risk for C, D, and X are based on risk and benefits to patient, not just risk
  - Categories do not distinguish differences in frequency, severity, and type of fetal toxicities
- Two subsections: pregnancy and lactation
  - Labor and delivery section eliminated
  - Three components: risk summary, clinical considerations, and data section

http://www.gpo.gov/fdsys/pkg/FR-2008-05-29/pdf/E8-11806.pdf

BREASTFEEDING AND MEDICATION USE

- Rates of breastfeeding in the US per CDC 2013 report card:
  - 77% infants begin life breastfeeding; 49% breastfeeding at 6 months, 27% at 12 months
- ~90% of women take some form of medication during the first week postpartum
  - In a study of 14,000 pregnant/breastfeeding women, 79% used meds while breastfeeding, avg intake: 3.9 drugs
- Maternal compliance with drug therapy can be erratic while breastfeeding secondary to infant concerns

DRUG TRANSFER INTO BREAST MILK

- Most drugs cross into breast milk but amount and concentration transferred are low and relatively safe for infant
- Maternal and infant characteristics influence amount of drug transferred into milk

MATERNAL FACTORS

- Dose and duration of therapy
  - Low dose, infrequent dosing, short duration
  - If drug contraindicated, may consider "pump and dump"
- Route of administration
  - Drugs given IV before of poor PO bioavailability are usually poorly absorbed by infant through milk
- Drug pharmacokinetics
  - Drugs with long half-life may result in cumulative exposure in infant

INFANT FACTORS

- Total amount of drug exposure to infant:
  - Concentration in breast milk and volume of milk ingested per day
- Gestational age and postnatal age determine infants ability to absorb, metabolize, and excrete drug
  - Preterm infant less able to metabolize and excrete drugs because of less mature liver and kidneys

PHARMACOKINETICS

- What the body does to the drug
- Describes the movement of drug into, through, and out of the body
  - Absorption: translocation of drug from site of administration into blood
  - Distribution: space within the body that drug must fill to reach steady-state
  - Metabolism: biotransformation of drug to metabolites
  - Excretion: removal of drug from the body
- Must consider both maternal and neonatal pharmacokinetic profiles to predict fetal/neonatal outcomes of medication use

ASHP Chapter. http://www.ashp.org/doclibrary/bookstore/p2418-chapter1.aspx

MATERNAL ABSORPTION

- Increased gastric emptying time
- Decreased intestinal motility
- Result: delayed absorption time, delayed peak effect, negligible effect on steady-state

MATERNAL DISTRIBUTION

- Body composition
  - Increase in maternal fat relatively constant with weight gain
  - Result: increased doses needed for fat-soluble drugs, accumulation may occur in adipose tissue (increased half-life, prolonged drug effects)
- Body volume
  - Increased total body water, extracellular water, and plasma volume
  - Increased cardiac output, heart rate, stroke volume
  - Result: decreased serum concentrations water-soluble drugs

MATERNAL DISTRIBUTION

- Serum proteins decreased
- Increased free fraction of highly bound drugs
- Result: increased exposure across placenta to protein-bound drugs

MATERNAL METABOLISM

- Increased hepatic enzyme activity
- Result: increased metabolism, clearance
  - Higher doses needed of drug to maintain effect

NEONATAL PHARMACOKINETICS

- Important clinical features
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

NEONATAL ABSORPTION

- Enteral
- Percutaneous
- Subcutaneous
- Intramuscular
- Intrapulmonary
- Rectal

NEONATAL ABSORPTION-ENTERAL

- Most drugs absorbed in small intestine
- Gastrointestinal pH, transit time, and gastric emptying play important roles in total drug exposure time and absorption
- Gastric acidity
  - Does not reach adult levels until 2-3 years of age
  - Introduction of nutrition helps regulate GI function
  - Acid production function of postnatal age, not PCA
  - Length/frequency of feeding can impact pH
  - Drugs that are weak acids absorbed more slowly than weak bases

NEONATAL ABSORPTION-ENTERAL

Table 1. Comparative Intestinal Variables Affecting Gastrointestinal Drug Absorption

Parameter	Full-term Newborn	1-day to 1-month-old Infant	1-month to 2-year-old Infant
Gastric pH	1-3	>5	Adult
Gastric Emptying time	Variable/reduced	Variable/reduced	Increased
Intestinal Transit Time	Reduced	Reduced	Increased
Intestinal Surface Area	Reduced	Reduced	~Adult
Bacterial Flora	Very limited	Limited	Developing
Transporter Maturity	Immature	Immature	Developing
Rectal Absorption*	Excellent	Excellent	Adult

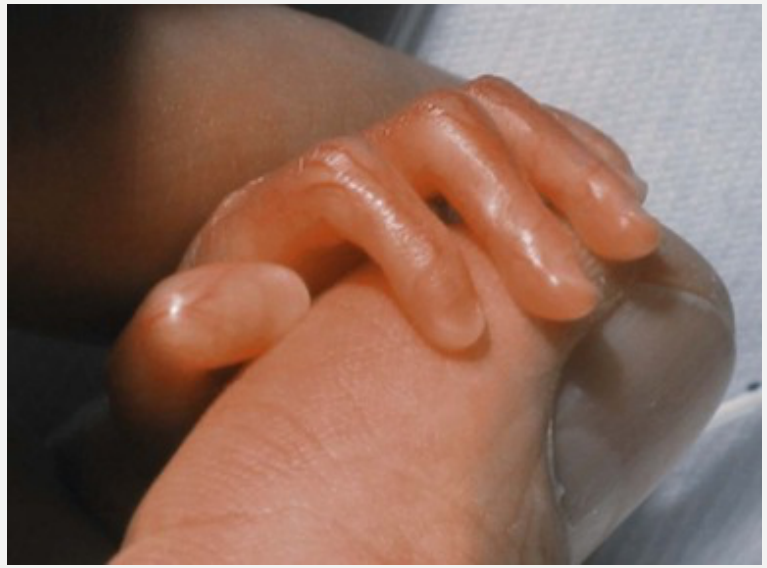
Tayman et al. JPPT 2011

FACTORS AFFECTING GASTRIC EMPTYING

- Gestational and postnatal age
- Increased:
  - Extensively hydrolyzed formula compared to intact or partially hydrolyzed
- Decreased:
  - Increasing caloric density and medium-chain triglycerides
- Does not approach adult times until 6-8 months of life

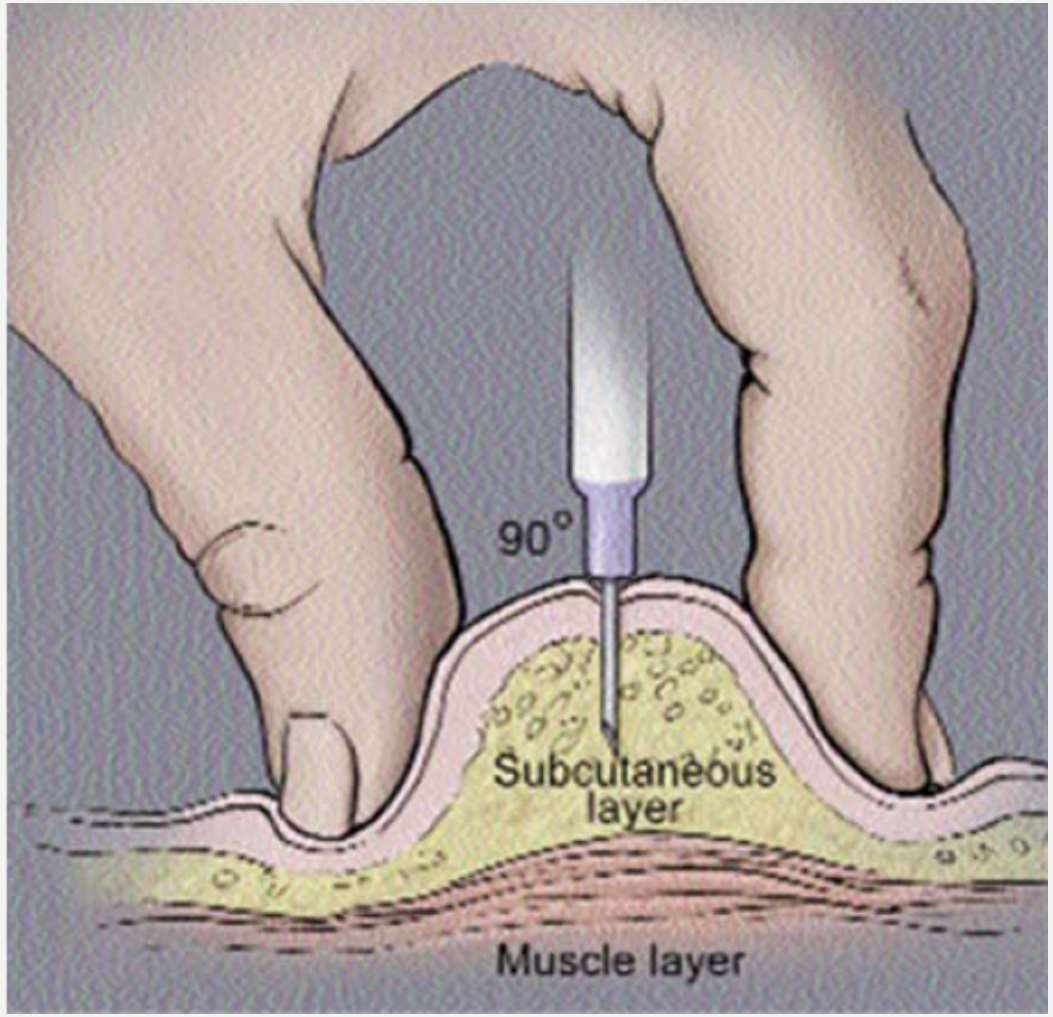
NEONATAL ABSORPTION- PERCUTANEOUS

- Degree of skin hydration and relative absorption surface area
  - Inversely related to thickness of stratum corneum
- Term infants
  - Intact skin barrier function
  - Ratio of surface area to body weight much higher than adults
  - 2.7 x greater amount drug exposure



NEONATAL ABSORPTION- SUBCUTANEOUS

- Subcutaneous injection goes into the fatty layer of tissue under the skin
  - Little blood flow to fatty tissue
  - Injected medication absorbed more slowly
- Premature neonates generally lack the fatty tissue of the subcutaneous space that makes this dosing method effective



NEONATAL ABSORPTION- INTRAMUSCULAR

- Physicochemical and physiologic factors affect rate
  - Drug pH, lipophilicity
  - Blood flow, total surface area of muscle at injection site
- Rate of absorption may be lower
  - Extent of absorption may be higher secondary to higher density of skeletal muscle capillaries compared to older children and adults

NEONATAL ABSORPTION-OTHER

Intrapulmonary

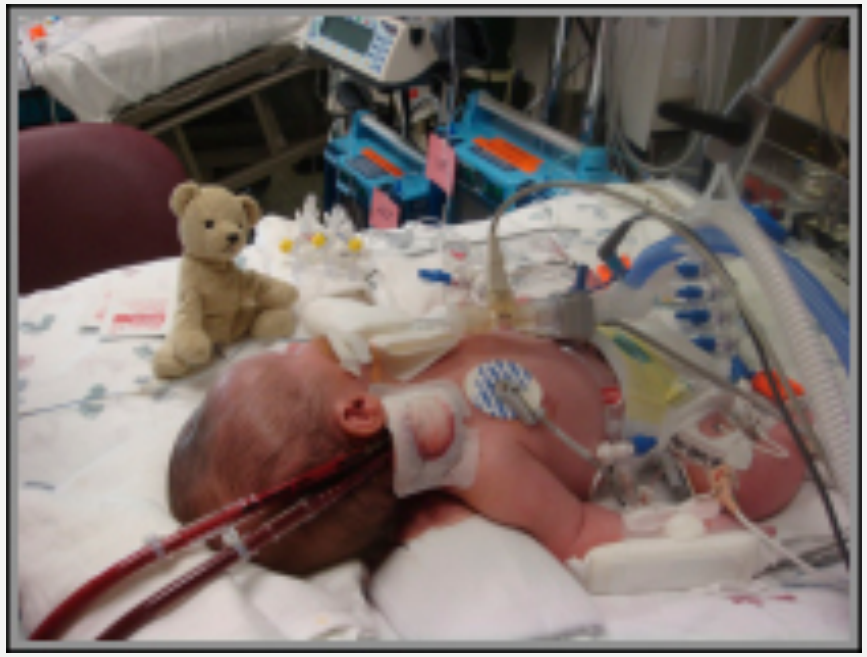
- Final stages of normal lung development interrupted in premature infants
  - Decreased lung volumes, gas exchange, capillary surface area
- Potentially altered patterns of drug disposition and absorption
  - Ventilatory type and settings (high-frequency vs. conventional)

Rectal

- Rapid, complete absorption
- Dosage formulations often problematic

NEONATAL DISTRIBUTION

- Occurs after reaching systemic circulation
- Factors affecting distribution:
  - Body compartment size and composition
  - Hemodynamics (cardiac output, regional blood flow)
  - Membrane permeability
  - Fat/water solubility of drugs
  - Plasma protein binding



NEONATAL DISTRIBUTION-PROTEIN BINDING

- Affinity of albumin for acidic drugs increases from birth to early infancy
- Alpha 1-acid glycoprotein binds basic drugs
  - Neonates have half the adult concentration
- Overall binding affinity lower
  - Increased free fraction of drug, increased availability of active compound
  - Increased adverse effects, increased drug clearance
- Free fatty acids and unconjugated bilirubin displace drugs from protein binding sites
  - Ampicillin, sulfonamides, phenytoin, diazepam

NEONATAL DISTRIBUTION-BODY COMPOSITION

- Physiologic space for drug distribution displays changes early in neonatal life
  - Ratio of total body water to body weight is greater in newborns
  - Total body fat lower (1% premature vs. 15-20% term)
- Higher weight-based doses of hydrophilic drugs needed
  - Aminoglycosides
- Lower weight-based doses of lipophilic drugs needed
  - Propofol

NEONATAL DISTRIBUTION-BLOOD COMPONENTS

- Blood flow
- Organ perfusion
- Cell membrane permeability
  - BBB more permeable in premature infants, passive diffusion of drugs
- Acid-base balance
- Cardiac output

DEVELOPMENTAL FLUID COMPARTMENTS

Patient Age	% of Total Body Water*	% of Extra-cellular Fluid*	% of Intra-cellular Fluid*
<3 month fetus	92	65	25
Term gestation	75	35-44	33
4-6 months	60	23	37
12 months	-	26-30	-
Puberty	~60	20	40
Adult	50-60	20	40

VOLUME OF DISTRIBUTION

Drug	Volume of Distribution (L/kg)	
	Neonate (1-30 days old)	Adult
Digoxin	8-10	7
Gentamicin	0.7-1.5	0.2-0.45
Ibuprofen	0.2-0.38	0.15
Indomethacin	2.5-4	1-1.5
Midazolam	1.2-2	0.8-2
Phenobarbital	0.8-1.2	0.5-0.6
Phenytoin	1.2-1.4	0.6-0.7

NEONATAL METABOLISM

- Action:
  - Conversion of drugs to water soluble metabolite for easier excretion
  - Inactive drug into active metabolite, toxic metabolite
- Sites of metabolism:
  - GI tract
  - Kidney
  - Liver
  - Lungs

NEONATAL METABOLISM

- Expression of intestinal drug metabolizing enzymes markedly different in neonates
  - Duodenal and jejunal CYP450 enzymes age-dependent (3A4, 1A1)
  - Other metabolic enzymes (epoxide hydrolase, glutathione peroxidase) demonstrate little dependence on age
  - Beta-glucuronidase in small intestine 7-fold higher in children
- Oral bioavailability impacted by GI enzyme expression

NEONATAL HEPATIC METABOLISM

- Overall rate of biotransformation of drugs much slower
  - Rapid physiologic changes occur in first week of life that change capacity of hepatic drug metabolism and oral bioavailability
    - Changes in hepatic blood flow, increased portal venous flow, closure of ductus venosus
- Phase I:
  - Oxidation, reduction, and hydrolysis
  - Mediated by cytochrome enzymes
- Phase II:
  - Conjugation pathways
  - Acetylation, glucuronidation, sulfation, methylation

PHASE I REACTIONS

- Total hepatic cytochrome P450 concentration is 30% adult values
  - All isoenzymes display age-dependent maturation
- CYP3A7 is major isoform present in fetus and neonate
  - Disappears 1-4 weeks after birth
  - CYP3A4 begins to overtake expression, reaching 30-50% adult levels at 3-12 months of age

DEVELOPMENT OF METABOLIC ENZYME ACTIVITY

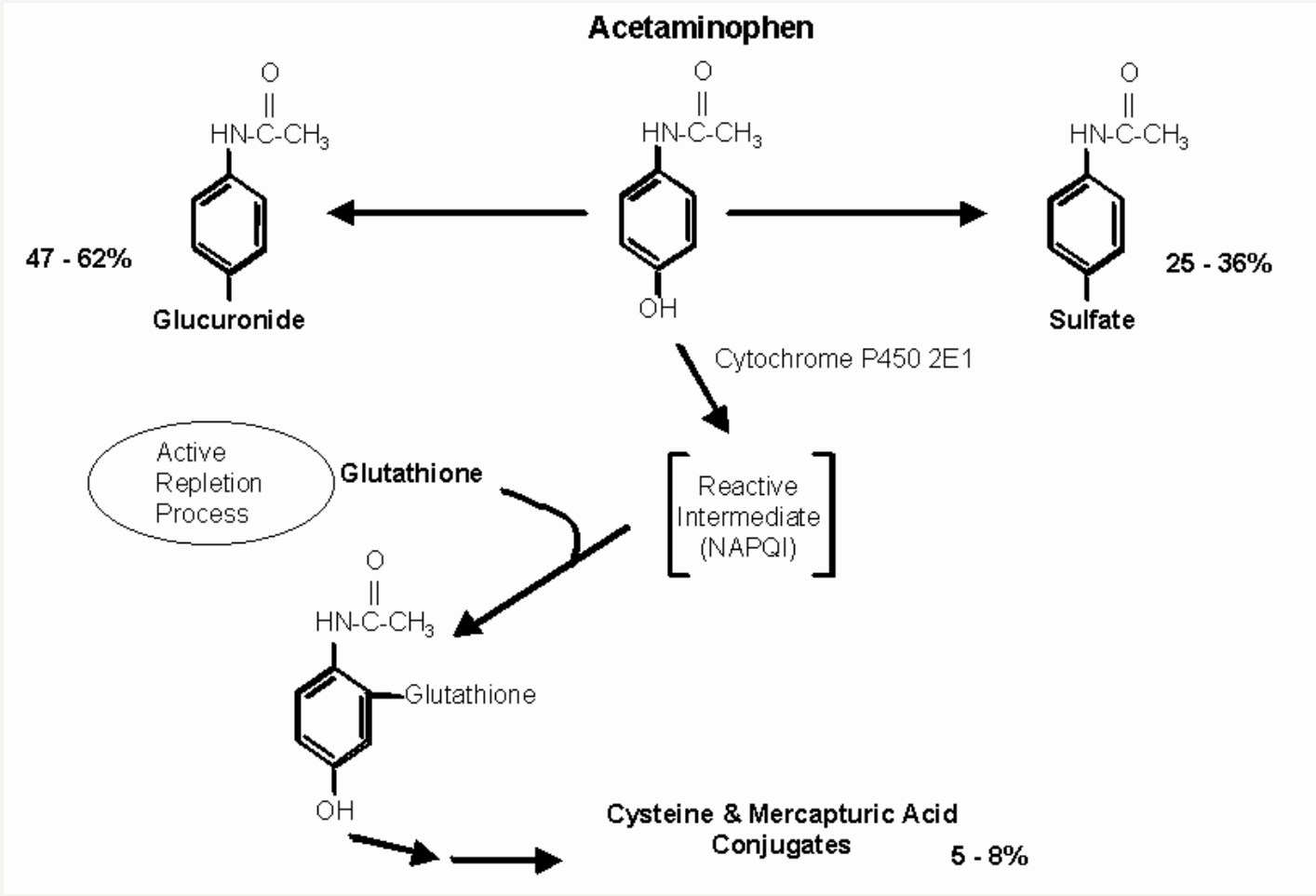
Table 7. Ontogenic Patterns of Pharmacologically Important Phase I/II Drug Metabolizing Enzymes

Drug	Fetal Liver*	1 month*	Time to Adult Activity
Phase I			
CYP 2D6	Low to absent	~20%	3-5 years
CPP 2C9/C19	Low to absent	Low	6 months
CYP 1A2	Low to absent	Low	4 months
CYP 3A4	Low to absent	30%-40%	6 months
Phase II			
NAT	Poor	Poor	
TPMT	~30% Adult	Highly variable†	1-3 years
UGT	Limited	Highly variable†	6-24 months
ST	Developed	Highly variable†	Isoform specific

PHASE II REACTIONS

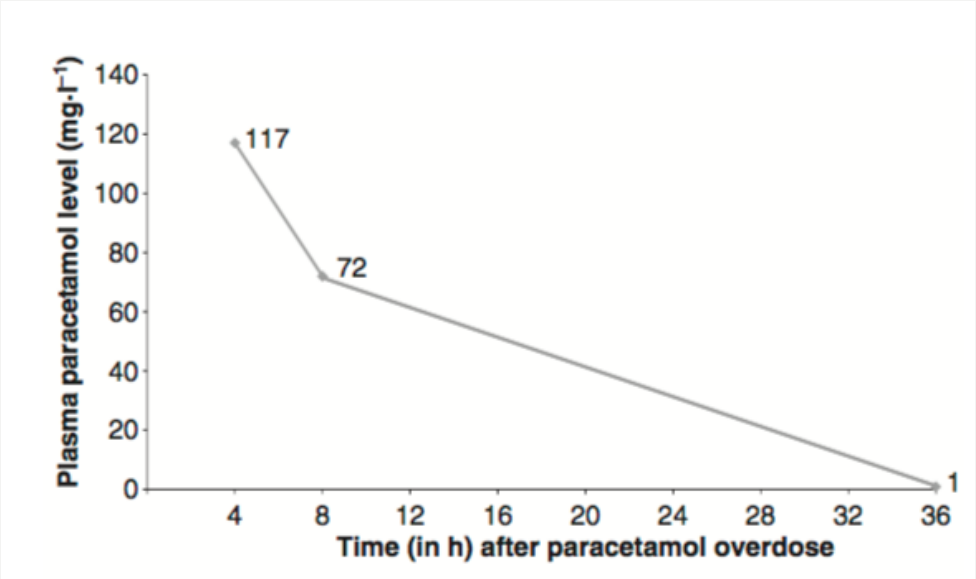
- Lack of data for impact of neonatal development on phase II enzymes
  - Appears to be age-dependent
- Clinical importance
  - Bilirubin UGT is immature in almost all neonates
  - Gray baby syndrome with chloramphenicol
  - Morphine metabolism
  - Paracetamol metabolism

ACETAMINOPHEN METABOLISM



ACETAMINOPHEN OVERDOSE IN PREMATURE NEONATES

- Eur J Clin Pharmacol 2012
  - 25.5 week GA infant (DOL 12) given 446 mg/kg
- Pediatric Anesthesia 2010
  - 28 week GA (35 weeks corrected) given 146 mg/kg
- Arch Dis Child Fetal Neonatal Ed 2001
  - 29 week GA (DOL 55) given 136 mg/kg
- NO hepatic toxicity seen in any patient
  - Due to slow oxidative metabolism and rapid glutathione synthesis



NEONATAL EXCRETION

- Renal excretion primary route for most drugs
  - Nonvolatile, water soluble, low molecular weight
- Three processes
  - Glomerular filtration
  - Tubular secretion
  - Active or passive tubular reabsorption
- Nephrogenesis
  - Begins at 9 weeks gestation, complete at 34 weeks gestation
  - May be impacted *in utero* by fetal growth retardation, maternal nephrotoxic medications, renal/urologic malformations

NEONATAL GLOMERULAR FILTRATION RATE

- GFR in first week of life
  - Preterm: 0.6 to 0.8 mL/min/1.73 m2
  - Term: 2 to 4 mL/min/1.73 m2
- Rapid increases in GFR over first 2 weeks of life
  - Drop in renal vascular resistance
  - Increase in renal blood flow
- Other factors influencing GFR
  - Vasoactive systems (RAAS)
  - Plasma protein concentration
  - Arteriolar resistance
  - Surface area of glomerular membrane

GENTAMICIN PHARMACOKINETICS

Baseline Demographics		
GA (wk)	Number of Patients	BW (g)
23	9	571.2
24	23	646.5
25	29	722.2
26	27	796.3
27	41	944.6
28	33	1014.4
29	41	1202.7

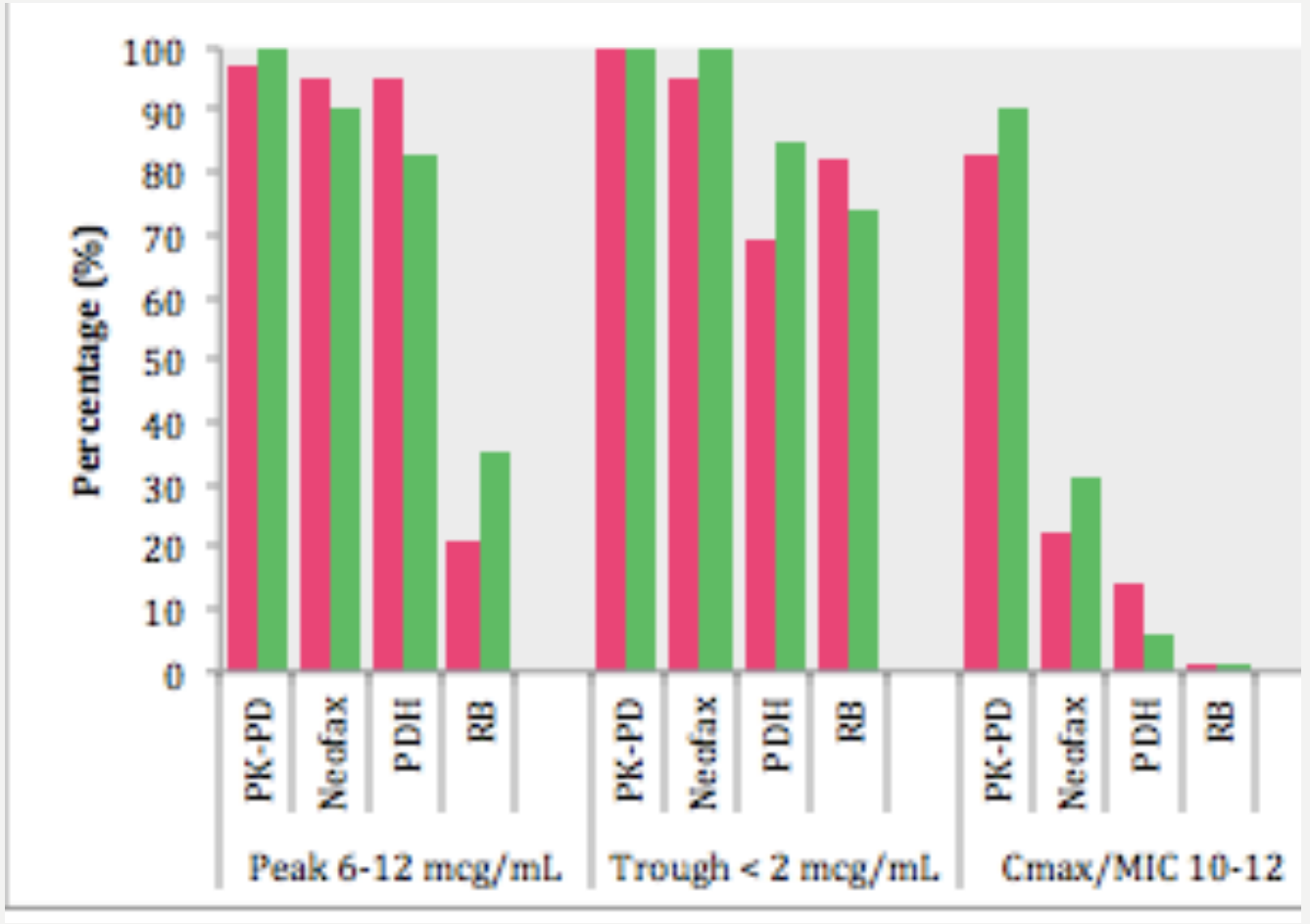
O'Mara et al. ASHP poster presentation 2007

GENTAMICIN PHARMACOKINETICS

GA (wk)	ke (hr-1)	Vd (L/kg)	Cl (mL/kg/min)	T ½ (hr)
23	0.069	0.53	0.036	12.9
24	0.058	0.58	0.035	12.5
25	0.056	0.60	0.033	13.2
26	0.061	0.58	0.038	11.8
27	0.069	0.56	0.040	10.3
28	0.076	0.54	0.045	9.6
29	0.073	0.58	0.043	9.7

O'Mara et al. ASHP poster presentation 2007

GENTAMICIN PHARMACOKINETICS



O'Mara et al. ASHP poster presentation 2007

NEONATAL TUBULAR SECRETION

- Immature at birth, approaches adult values at 7-12 months
- Limited tubular function in premature neonates
  - Renal elimination of pencillins, cephalosporins
- Active transport process dependent on:
  - Blood flow
  - Affinity of drug carrier proteins in proximal tubule
  - Rate of transport across tubular membranes
  - Rate of delivery of drug to the site of secretion

PHARMACOKINETICS OF AMPICILLIN IN NEONATES

TABLE 1 Demographic characteristics[a]

	Value for the indicated gestational age (wk) and PNA (days)				
	≤34		>34		
Parameter	≤7	8–28	≤7	8–28	Total
Group no.	1	2	3	4	
n	21	7	27	18	73
Postnatal age (days) at day of first plasma PK sample					
Mean (SD)	2.6 (2.3)	15.4 (4.0)	2.9 (2.6)	13.4 (5.4)	6.6 (6.4)
Median (minimum, maximum)	1.0 (0.0, 7.0)	16.0 (9.0, 21.0)	2.0 (0.0, 7.0)	12.5 (8.0, 25.0)	5.0 (0.0, 25.0)
Gestational age (wk)					
Mean (SD)	30.3 (3.4)	26.9 (2.5)	38.2 (2.0)	38.4 (1.8)	34.9 (5.0)
Median (minimum, maximum)	32.3 (24.0, 34.0)	26.1 (25.0, 32.0)	38.0 (34.0, 41.0)	38.8 (35.0, 41.0)	36.1 (24.0, 41.0)
No. (%) male	9 (43)	3 (43)	18 (67)	8 (44)	38 (52)
Ethnicity, no. (%)					
Hispanic or Latino	3 (14)	1 (14)	6 (22)	3 (16)	13 (18)
Not Hispanic or Latino	18 (86)	5 (71)	19 (70)	14 (78)	56 (77)
Not reported	0	1 (14)	2 (7)	1 (6)	4 (6)
Race, no. (%)					
Black	4 (19)	3 (43)	3 (11)	2 (11)	12 (16)
White	16 (76)	3 (43)	23 (85)	14 (78)	56 (77)
Not reported	0	0	0	1 (6)	1 (1)
Other	1 (5)	1 (14)	0	1 (6)	3 (4)

[a] PK, pharmacokinetic; PNA, postnatal age.

PHARMACOKINETICS OF AMPICILLIN IN NEONATES

TABLE 5 Individual empirical Bayesian *post hoc* parameter estimates[a]

Group	*n*	Clearance (liters/h/kg)	Volume (liters/kg)	Half-life (h)	Steady-state concn (μg/ml)	
					Minimum	Maximum
1	21	0.055 (0.03–0.07)	0.40 (0.40–0.40)	5.0 (3.9–9.4)	77 (36–320)	318 (244–563)
2	7	0.070 (0.03–0.07)	0.40 (0.40–0.41)	4.0 (3.8–8.3)	33 (21–145)	266 (159–368)
3	27	0.086 (0.04–0.13)	0.40 (0.40–0.40)	3.2 (2.2–6.2)	48 (5–173)	274 (127–413)
4	18	0.11 (0.06–0.13)	0.40 (0.40–0.41)	2.4 (2.1–4.7)	28 (5–129)	246 (138–203)
Overall	73	0.072 (0.03–0.13)	0.40 (0.40–0.41)	3.3 (2.1–9.4)	47 (5–320)	281 (127–563)

[a] All values are medians and ranges.

PHARMACOKINETICS OF AMPICILLIN IN NEONATES

TABLE 7 Optimal dosing regimen based on Monte Carlo simulations using the final pharmacokinetic model

Gestational age (wk)	Postnatal age (days)	Maintenance dose (mg/kg)	Dosing interval (h)
≤34	≤7	50	12
≤34	≥8 and ≤28	75	12
>34	≤28	50	8

NEONATAL TUBULAR REABSORPTION

- Immature at birth, especially in preterm infants
  - Development and maturation of glomerular permeability functions and renal tubular reabsorption are gradual process
  - Peak maturation at 1-3 years
- Depends on physiochemical characteristics of drugs
  - Lipophilicity
  - Water solubility
  - Acidic vs. basic pH
  - pH of fluids in proximal and distal tubules

DISEASE STATES THAT IMPACT DRUG BEHAVIOR

- Extremely premature birth
- Peripartum asphyxia
- Therapeutic hypothermia
- Extracorporeal membrane oxygenation
- Sepsis
- Patent ductus arteriosus
- Necrotizing enterocolitis

PDA IMPACT ON PK

- PK differences between neonates with significant PDA vs. no PDA

Variable	Control (n = 216)	Patent Ductus Arteriosus (n = 106)	*p* Value
Ke (hr)	0.8 ± 0.02	0.06 ± 0.03	.0001
$T_{1/2}$ (hr)	8.98 ± 2.86	12.24 ± 7.43	.0001
Vd (L/kg)	0.54 ± 0.13	0.61 ± 0.15	.0002
CL (mL/kg/hr)	44.73 ± 14.74	40.02 ± 16.85	.0108

Ke, elimination constant; $T_{1/2}$, half-life; Vd, volume of distribution; CL, clearance.

Williams et al. Crit Care Med 1997

PDA: Patent ductus arteriosus

VOLUME OF DISTRIBUTION WITH PDA

Vd (L/kg)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0.6	48	75	48	75
0.65	32	86	53	72
0.7	24	92	60	71
0.75	17	95	62	70
0.8	10	96	58	69

Williams et al. Crit Care Med 1997

Vd: volume of distribution
PPV: positive predictive value
NPV: negative predictive value

CONCLUSIONS

- Neonatal response to drug therapy is multi-factorial
  - Maternal factors
  - Gestational age
  - Postnatal age
- Maturational differences in pharmacokinetic profiles leads to different efficacy and toxicity profiles compared to other patient populations
  - Importance of understanding timeline of development of metabolic enzymes and clearance pathways