Developmental Pharmacology

Scaling adult doses to infants based on body weight or surface area does not account for developmental changes that affect drug disposition or tissue/organ sensitivity.

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Chloramphenicol

Chemical structure of Chloramphenicol

Natural product of *Streptomyces* (1947)

Inhibits protein synthesis (bacteriostatic)

Eliminated by glucuronide conjugation (90%) and renal excretion (<10%)

Nursery infections treated with high doses

Chloramphenicol in Infants

3320 gm infant, 44 week gestation

Meconium stained, foul smelling, timing of ROM unknown

Procaine penicillin (50,000 units) + chloramphenicol (250 mg) IM q8h - 230 mg/kg/day x 72 hr

Day 4, gray color & cold, moist skin

Died at 106 hr, 8 hr after onset of vascular collapse

Sutherland, Am J Dis Child 97:761-7, 1959

Chloramphenicol in Premature Infants

Premature infants born ≥24 hrs after ROM

	All Infants		2001-2500 gm	
	N	Deaths	n	Deaths
No antibiotics	**32**	**6**	**17**	**1**
Pen + strep	**33**	**6**	**24**	**0**
Chloramphenicol	**30**	**19**	**16**	**8**
Pen + strep + Chloramphenicol	**31**	**21**	**15**	**6**

Burns et al., NEJM 261:1318-21, 1959

Gray Baby Syndrome

List of symptoms in infants with the % having those symptoms with no antibiotics, or pen & strep or chloramphenicol. The frequency is highest for Chloramphenicol (4 – 5.7%).

Jaundice
Vomiting
Anorexia
Resp. distress
Abd. Distention
Cyanosis
Green stools
Lethargy
Ashen color
Death

Burns et al., NEJM 261:1318-21, 1959

Chloramphenicol Blood Levels

Chloramphenicol doses

Line chart showing the total nitro compounds [µg/ml] over day of life increasing with multiple doses, and the therapeutic range.

Burns et al., NEJM 261:1318-21, 1959

Chloramphenicol Pharmacokinetics

Line chart showing declining total Nitro compounds [µg/ml] over time [hr] in neonates, ($T_{½}$ = 26 hrs), infants ($T_{½}$ = 10 hrs) and children ($T_{½}$ = 4hrs).

Weiss et al., NEJM 262:787-94, 1960

Repeated Administration

Scatter chart showing Total Nitro Compounds [µg/ml over Day of Life. Levels decline as infant develops.

Weiss et al., NEJM 262:787-94, 1960

Drug Use in Infants and Children

Scaling adult doses based on body weight or surface area does not account for developmental changes that affect drug disposition or tissue/organ sensitivity.

Pharmacologic impact of developmental changes are often discovered when unexpected or severe toxicity in infants and children leads to detailed pharmacologic studies.

Therapeutic tragedies could be avoided by performing pediatric pharmacologic studies during the drug development process (before wide-spread use of agents in infants and children).

Zidovudine

Chemical structure of Zidovudine

Synthetic nucleoside analog

Inhibits HIV reverse transcriptase

Eliminated by glucuronide conjugation (67%) and renal excretion (33%)

Perinatal therapy to prevent HIV transmission

Zidovudine in the Newborn

Scatter chart showing **ZDV AUC [µg x hr/ml] over Age [weeks].**

Drug exposure decreases with increasing infant age.

Boucher et al., J Pediatr 122:137-44, 1993

Zidovudine in Newborns

Group	Age (days)	Clearance (ml/min/kg)	$t_{1/2}$ (hr)	F (%)
Preterm	5.5	2.5	7.2	
	17.7	4.4	4.4	
Term	[2]14	10.9	3.1	
	>14	19.0	1.9	

Age Group	Clearance (ml/min/kg)	$t_{1/2}$ (hr)	F (%)
1-13 yrs	24	1.5	68
Adults	21	1.1	63

Balis et al., J Pediatr 114:880-4, 1989
Klecker et al., Clin Pharmacol Ther 41: 407-12, 1987

Boucher et al., J Pediatr 125:642-9, 1994
Mirochnick et al., Antimicrob Agents Chemother 42:808-12, 1998

Prevention of Vertical Transmission

Randomized, double-blind, placebo controlled trial

Rate of vertical transmission was the primary endpoint

Zidovudine/placebo regimen

Mothers: 100 mg of ZDV antepartum orally, 5 times daily, and then continuous infusion of 1 mg/kg/hr during labor and delivery

Infants: 2 mg/kg orally every 6 hours for 6 weeks, beginning 8-12 hours after birth.

Prevention of HIV Transmission

Chart showing the HIV-infected rate (%) of infants over 32 weeks of age and HIV-infected rate (%) for children age 1 year, comparing zidovudine and placebo treatments.

Chart showing age [weeks] of infants and their Hemoglobin [g/dl] levels when taking Zidovudine and when taking a placebo

Connor et al., NEJM 331:1173-80, 1994

Ontogeny and Pharmacology

Excretory organ (liver and kidneys) development has the greatest impact on drug disposition (pharmacokinetics)

The most dramatic changes occur during the first days to months of life

Anticipate age-related differences in drug disposition based on knowledge of ontogeny

Effect of ontogeny on tissue/organ sensitivity to drugs (pharmacodynamics) is poorly studied

Disease states may alter a drug's PK/PD

Renal Ontogeny

Glomerular filtration rate

Low at birth

Full term newborn - 10-15 ml/min/m^2
Premature - 5-10 ml/min/m^2

GFR doubles by 1 week of age

Adult values by 6-12 months of age

Tubular function

Secretory function impaired at birth

Glomerulotubular imbalance

Adult values by 1 year of age

Glomerular Filtration Rate

Graph (scatter chart) showing GFR [ml/min/1.73 m^2] in infants at various ages [months]
GFR increases with age.

Aperia, Acta Pædiatr Scand 64:393-8, 1975

GFR in Infants

Scatter chart showing GFR [ml/min/1.73 m^2] over age [days] of infants.
GFR increases with age.

Guignard, J Pediatr 87:268-72, 1975

Gentamicin Clearance

Bar chart showing the postnatal age and gentamicin clearance [L/kg x hr] in premature (< 37 weeks) and full term infants

Clearance increases with age.

Pons, Ther Drug Monit 10:421-7, 1988

Hepatic Ontogeny

Phase 1 (oxidation, hydrolysis, reduction, demethylation)

- **Activity low at birth**
- **Mature at variable rates**
  - Oxidative metabolism increases rapidly after birth
  - Alcohol dehydrogenase reaches adult levels at 5 yrs
- **Activity in young children exceeds adult levels**

Phase 2 (conjugation, acetylation, methylation)

- **Conjugation:**
  - Glucuronidation ↓ at birth
  - Sulfatation ↑ at birth
- **Acetylation ↓ at birth, "fast" or "slow" phenotype by 12-15 mo.**

Cytochrome P450 (CYP) Enzymes

Superfamily of Phase 1 enzymes (oxidation, demethylation)

Nomenclature:

Family (>40%)------↓ ↓------Subfamily (>55%)

CYP3A4
↓__**Isoform**

17 Families and 39 subfamilies in humans

CYP1, CYP2, CYP3 are primary drug metabolizing enzymes

Half of all drugs metabolized by CYP3A subfamily

CYP3A4 is most abundant hepatic P450 enzyme and metabolizes at least 50 drugs

CYP Ontogeny

Ontogeny of CYP Enzymes

Bar chart showing the percent of adult activity in CYP3A4, CYP1A2, CYP2D6 and UGT2B7 at different times (<24 hr, 1-7 days, 8-28 days, 1-3 mo, 3-12 mo, and 1-10 yr.)

Kearns GL et al. NEJM 349: 1157, 2003

CYP2E1 Ontogeny

Bar chart showing CYP2E1 │% Adult Level│ at 3rd trimester, 0-30 days, 31-90 days, and 91 days – 18 years.

CYP3A Ontogeny

CYP3A7 Activity and CYP3A4 Activity at < 30 w, >30w, <24 h, 1-7 d, 8-28 d, 1-3 mo, 3-12 mo, > 1 yr and in adults.

LaCroix D et al. Eur J Biochem 247:625, 1997

Acetaminophen Metabolism

Bar chart showing % of dose of acetaminophen, Glucuronide, and Sulfate in newborns, children 3-9 years, 12 years, and for adults.

Miller et al., Clin Pharmacol Ther 19:284-94, 1976

Theophylline Urinary Metabolites

Chart showing post-conception age and age range of the % of theophylline, caffeine, 3-Mex, 1-MeUA, and 1,3-diMeUA recovered in urine.

Factors Affecting Drug Distribution

Physicochemical properties of the drug

Cardiac output/Regional blood flow

Degree of protein/tissue binding

Body composition

- **Extracellular water**
- **Adipose tissue**

Ontogeny of Body Composition

Chart showing the % of total body weight for extracellular and intracellular mater, protein, and fat at different ages from premature infants to adults.

Kaufman, Pediatric Pharmacology (Yaffe & Aranda, eds) pp. 212-9, 1992

Volume of Distribution of Sulfa

Chart showing the volume of distribution [L/kg] of sulfa in newborns, infants, children, adults and the elderly.

Volume of distribution is larger in newborns and infants.

Routledge, J Antimicrob Chemother 34 Suppl A:19-24, 1994

Tissue and Organ Weight

Chart showing the % of total body weight of skeletal muscle, skin, skeleton, heart, liver, kidneys, and brain in the fetus, newborn and adult

Plasma Proteins

Chart showing the change from adult values for newborns, infants and children of total protein, albumin, ∂_1-Acid glycoprotein, fetal albumin, and globulin.

Protein Binding in Cord and Adult Plasma

Chart showing plasma protein binding (%) in cord and in adult of acetaminophen chloramphenicol, morphine, Phenobarbital, phenytoin and promethazine.

Kurz et al., Europ J Clin Pharmacol II:463-7, 1977

CSF MTX and Age

Scatter chart showing CSF methotrexate [μM] over time [days] in adults, adolescents and children

Bleyer, Cancer Treat Rep 61:1419-25, 1977

CNS Growth and Development

Chart showing CNS volume and body surface area as % of adult values at various ages [years]

Bleyer, Cancer Treat Rep 61:1419-25, 1977

Adaptive IT MTX Dosing Regimen

Chart showing IT MTX dosing regimen based on at age [yrs] and MTX dose [MG].

Bleyer, Cancer Treat Rep 61:1419-25, 1977

Dose Change with Adaptive Regimen

Chart showing % change in dose at age [years] at 1.5 yrs, 4 yrs, 7 yrs , 10 yrs, and 13 yrs.

Bleyer, J Clin Oncol 1:317-25, 1983

Effect of Adaptive IT Dosing on Outcome

Two charts showing incidence of CNS relapse [%] of MTX dose based on BSA and MTX dose based on age in months at <18, 18-35, 36-83, 84-119, ≥ 12

Bleyer, J Clin Oncol 1:317-25, 1983

Dosing Based on Body Surface Area

BSA = 2-dimensional surface area of the skin

Estimated from formulas using weight & height

Correlation between BSA and kidney/liver function is weak

BSA dosing evolved from scaling doses from animals to humans (toxicology)

Chart

Pinkel, Cancer Res 18:853, 1958

Liver Function (Children)

Scatter chart showing liver Vol [ml] versus BSA │m^2│ and another scatter chart showing Antipyrine CL │ml/min│versus BSA │m^2│

Murry et al. Drug Metab Disp 23:1110, 1995

Excretory Organ Growth

Three line charts showing excretory organ (liver and kidney) growth by age │yr│

Body Weight:Surface Area

Graph showing $\frac{\text{weight}}{\text{BSA}}$ over age [yrs]

Adult
1 mg/kg = 40 mg/m2
Dose = 70 mg

1 y.o.
1 mg/kg = 10 mg
40 mg/m2 = 18 mg

Anticancer Drug Clearance

Chart showing a list of drugs including Methotrexate, Mercaptopurine, Vincristine, VM26/VP16, Doxorubicin and Cytarabine, their routes of elimination, CLinfants VS CL children and dosing.

Vincristine Clearance

Two charts showing vincristine clearance in adolescents, children and infants in ml/min/m^2 and ml/min/kg.

Crom et al., J Pediatr 125:642-9, 1994

Etoposide Clearance

Chart showing etoposide clearance [ml/min/m^2] and etoposide clearance [ml/min/kg] for infants of <1 yr (n=5) and children > 1 yr (n=25).

Doxorubicin Clearance

Chart showing Doxorubicin clearance [ml/min/m^2] and Doxorubicin clearance [ml/min/kg] for infants of <2 yr (n=8) and children > 1 yr (n= 52).

Oral Busulfan (16-30 mg/kg)

Scatter chart showing Busulfan C_{ss} [ng/ml] in children age 10 through adults age 60 which highlights engraftment and graft rejection.

Slattery et al., Bone Marrow Transplant 16:31, 1995

Drug Clearance in Cystic Fibrosis

Chart showing drug clearance [ml/min x m^2] in ibuprofen, Furosemide (NR), Theophylline, Cloxacillin (NR), Ceftazidime, Ticarcillin and Gentamycin

Rey, Clin Pharmacokinet 35:313-29, 1998

Retinoids

	≤12 Yr.	>12 Yr	Adult
ATRA			
MTD	**60 mg/m2/d**	**90 mg/m^2/d**	**150 mg/m^2/d**
DLT	**Pseudotumor cerebri**	**HA and PC**	**Dermatologic**
9-cis-RA			
MTD	**35 mg/m^2/d**	**85 mg/m^2/d**	**140 mg/m^2/d**
DLT	**Pseudotumor cerebri**	**HA and PC**	**HA, diarrhea, dermatologic**

Conclusions

Infants (esp. newborns) may have reduced capacity to eliminate drugs

Anticipate the effects of ontogeny on drug disposition based on route of elimination

More systematic pharmacokinetic studies of drugs in infants are needed

Tissue sensitivity to the toxic effects of drugs may be age-dependent

Cytochrome P450 Enzymes

Present in Fetus		Appear After Birth	Appear 3-4 Months of Age
CYP3A7*	→	CYP3A4*	
CYP1A1		CYP2D6	
CYP3A5		CYP2C9	
		CYP2C18/19	
		CYP2E1	

*Most abundant form

Gentamicin in the Newborn

Scatter chart showing Gentamicin clearance [ml/kg x hr] in 15 full term infants and 23 premature infants

Koren et al., Clin Pharmacol Ther 38:680-5, 1985