Therapeutics: Children Are not Little Adults!

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Learning Objectives

The student should be able to do the following :

- **Explain the difference between children and adults in drug exposure, drugs' pharmacokinetics, drugs' efficacy and toxicity**
- **Demonstrate how to check for drug's pregnancy category**
- **Demonstrate how to check for drug's breast feeding compatibility**
- **Demonstrate how to adjust dose according to renal or liver disease**
- **List the steps of prescribing a drug to a pediatric patient**

Pediatrics' Therapeutics

- Children take medications, many of which have not been proven safe and effective for their use.

- Children respond to medications differently from adults; thus, medicines must be studied in children and formulated for children.

Only $\frac{1}{4}$ of pediatrics' used drugs are approved by the FDA

Children are not Little Adults!

- Different & Unique Exposures @ a critical period
- Dynamic Developmental Physiology
- Longer Life Expectancy
- Politically Powerless

Different And Unique Exposures

Unique exposure pathways

- Tran placental
- Breastfeeding

Exploratory behaviors leading to exposures

- Hand-to-mouth, object-to-mouth
- Non-nutritive ingestion

Different And Unique Exposures

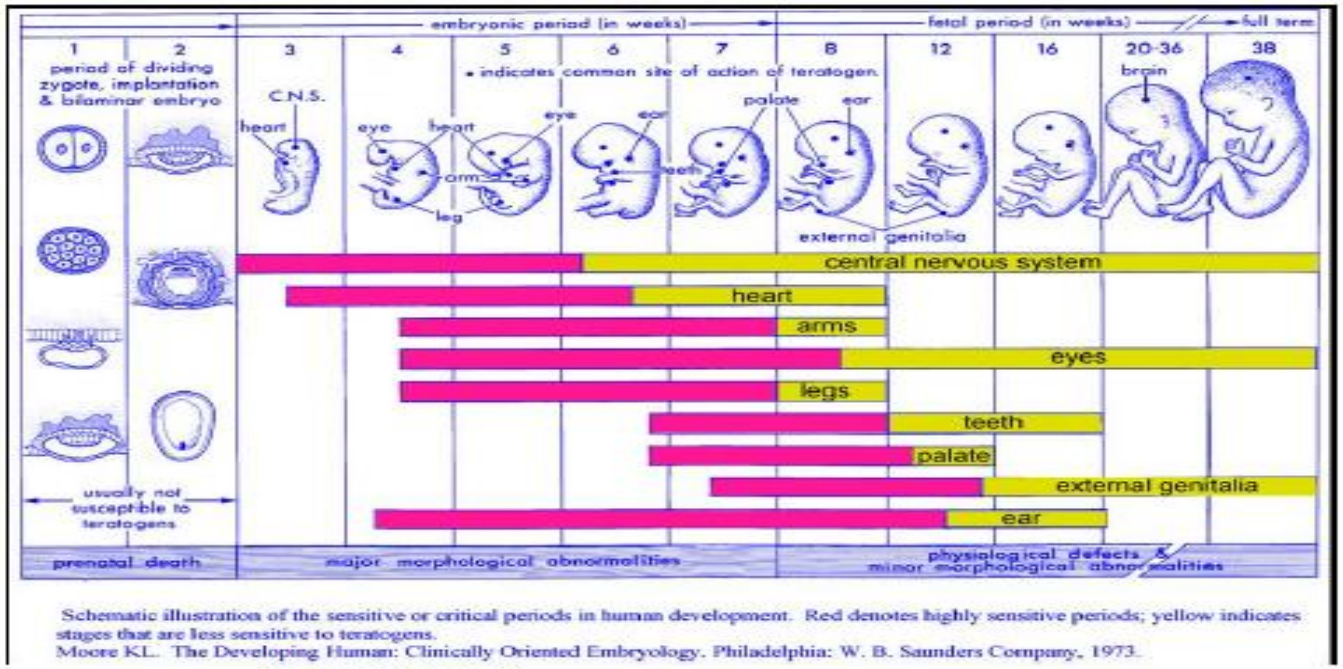
Stature and living zones, microenvironments

- Location – lower to the ground
- High surface area to volume ratio

Children do not understand danger

- Pre-ambulatory
- Adolescence – "high risk" behaviors

Critical Periods of Development: Preconception, embryonic ,postnatal



Schematic illustration of the sensitive or critical periods in human development. Red denotes highly sensitive periods; yellow indicates stages that are less sensitive to teratogens.
Moore KL. The Developing Human: Clinically Oriented Embryology. Philadelphia: W. B. Saunders Company, 1973.

Moore, Elsevier Inc, 1973

Trans placental exposure

- In order for a drug to cause a teratogenic or pharmacological effect on the fetus, it must cross from maternal circulation to fetal circulation through the placenta by diffusion

- Trans placental transfer of drugs increases in the third trimester due to increased maternal and placental blood flow, decreased thickness and increased surface area of the placental

Trans placental exposure

The rate of transfer depends on the chemical properties of the drug

- **Protein binding:** only free unbound drugs cross the placenta (maternal albumin increases)
- **pH difference:** fetal pH is slightly more acidic than maternal (weak bases are more likely to cross)
- **Lipid solubility:** Moderately lipid soluble drugs can easily diffuse across the placental membrane
- **Molecular weight** :Drugs with low molecular weight (<500 g/mol) diffuse freely across the placenta

Trans placental Exposure

How Drugs Affect the Fetus

- Death
- Birth defects
- IUGR : Alter the function of the placenta (constricting blood vessels and reducing the blood supply of oxygen and nutrients)
- Preterm delivery: muscles of the uterus contract forcefully (reducing the blood supply)

THALIDOMIDE TRAGEDY

- Sleeping pills post war
- The only non-Barbiturate sedative

- Europe OTC (the wonder drug)

- 1957 They advertised their product as “completely safe” for everyone, including mother and child, “even during pregnancy,” as its developers “could not find a dose high enough to kill a rat.”

- By 1960, thalidomide was marketed in 46 countries, with sales nearly matching those of aspirin

THALIDOMIDE TRAGEDY

- Dr. William McBride Australia : off- label for morning sickness

- 1961 German newspaper reported 160 newborn with phocomelia

THALIDOMIDE TRAGEDY

- USA : Dr Kelsey (FDA) refused to approve the drug
- Motivate profound changes in the FDA.
- The Kefauver-Harris Drug Amendments Act in 1962, requiring that manufacturers prove they are both safe and effective before they are marketed.
- Drug approval can take between eight and twelve years, involving animal testing and tightly regulated human clinical trials

Trans placental exposure

Diethylstilbestrol (DES):

- Clear cell carcinoma (vaginal tumor)
- 1971 NEJM published appear reporting 6/7 young girls with ccc were exposed to DES in utero.
- DES daughters
- DES sons

Trans Placental Exposure

- A study in 2001 found that there was not enough information about the risk or safety of more than 90% medications approved by FDA between 1980 and 2000 when taken during pregnancy.

- About 2-3% of all birth defects result from use of drugs

Classification of drugs according to safety in pregnancy

IV. EXPLANATION OF PREGNANCY CATEGORIES

A Adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.

B Animal studies have not demonstrated a risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus during the first trimester of pregnancy, and there is no evidence of risk in later trimesters.

C Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.

D There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

X Studies in animals or humans demonstrate fetal abnormalities or adverse reaction; reports indicate evidence of fetal risk. The risk of use in pregnant women clearly outweighs any possible benefit.

Breast feeding & drugs

- Most nursing mothers don't take any medications
- All drugs are virtually expressed in breast milk
- Most drugs are safe during breast feeding
- Most drugs are expressed in breast milk in a very little amount that don't pose any danger on the newborn
- The first 2 months of life are with highest risks
- Few drugs are contraindicated

Effect of drugs expressed in breast milk

Expression in breast milk

- Maternal plasma concentration
- Maternal protein binding
- Size of drug molecule
- Degree of ionization
- Lipid solubility
- Maternal pharmacogenomics
- Timing of the dose

Infant's factors

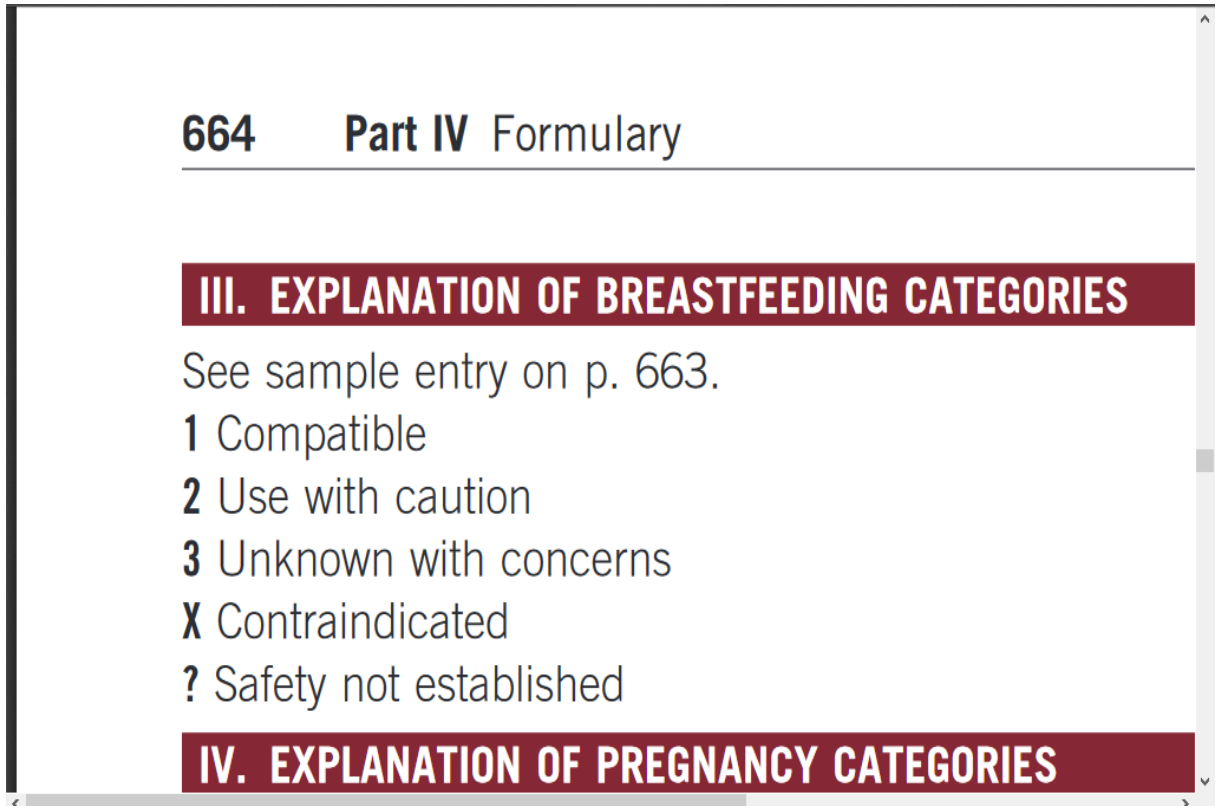
- Oral bioavailability
- Volume of breast milk
- Relative infant dose
- Age of infant

Table

Examples of drugs contraindicated in breastfeeding

Drug	Comment
Amiodarone	Long half-life, iodine-containing molecule, and may affect thyroid function in infant
Antineoplastics	Leukopenia, bone marrow suppression
Gold salts	Rash, nephritis, haematological abnormalities
Iodine	High doses (>150 micrograms daily) lead to risk of infant hypothyroidism
Lithium	Breastfeeding only feasible with rigorous monitoring
Radiopharmaceuticals	Contact obstetric information service
Retinoids (oral)	Potential for serious adverse effects

Classification of drugs safety with breast feeding



664 **Part IV** Formulary

III. EXPLANATION OF BREASTFEEDING CATEGORIES

See sample entry on p. 663.

1 Compatible

2 Use with caution

3 Unknown with concerns

X Contraindicated

? Safety not established

IV. EXPLANATION OF PREGNANCY CATEGORIES

II. SAMPLE ENTRY

Pregnancy: Refer to explanation of pregnancy categories (see p. 664).
Breast: Refer to explanation of breastfeeding categories (see p. 664).
Kidney: Indicates need for caution or need for dose adjustment in renal impairment (see also Chapter 31).
Liver: Indicates need for caution or need for dose adjustment in hepatic impairment.

How supplied

ACETAZOLAMIDE ← Generic name

Diamox and other generics ← Trade name and other names
Carbonic anhydrase inhibitor, diuretic ← Drug category

Tabs: 125, 250 mg
Oral suspension: 25 mg/mL ← Mortar and pestle: Indicates need for extemporaneous compounding by a pharmacist
Capsules (sustained release): 500 mg
Injection (sodium): 500 mg/5 mL
Contains 2.05 mEq Na/500 mg drug

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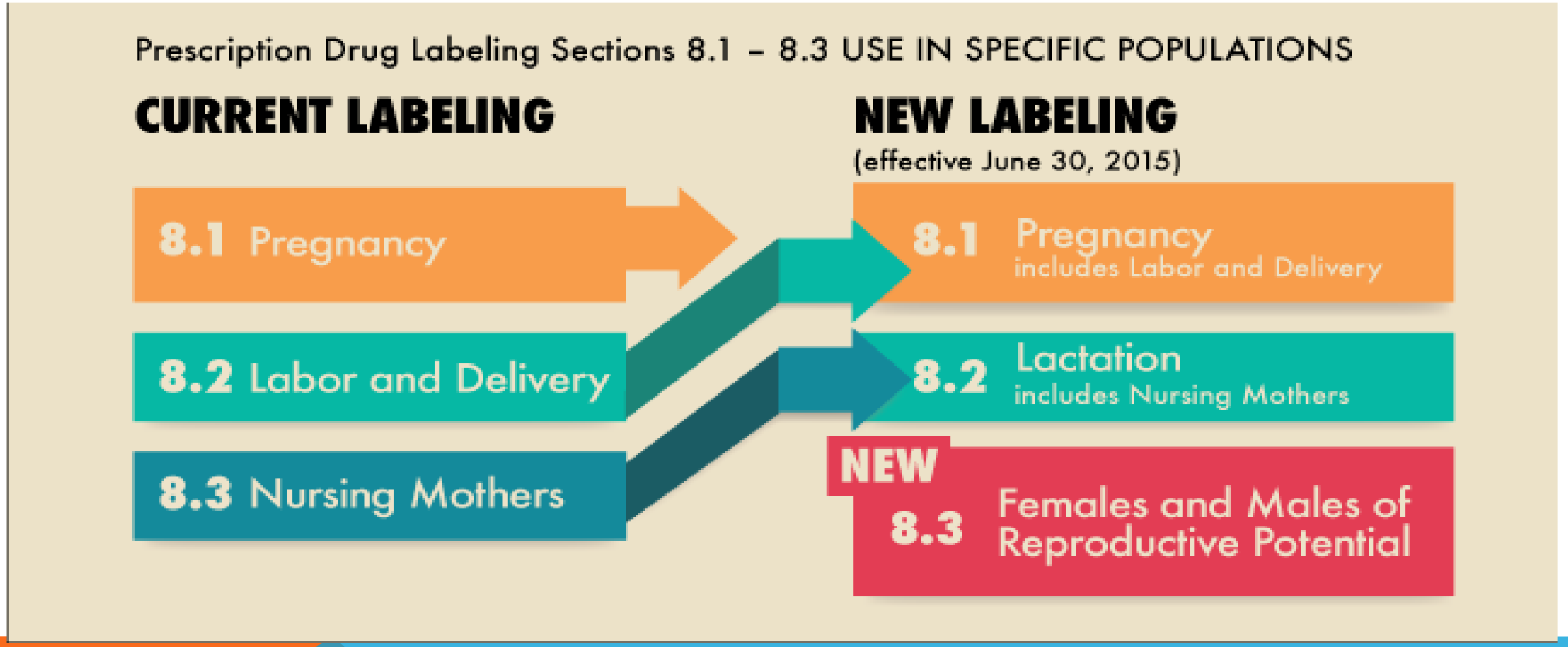
Diuretic (PO, IV)
Child: 5 mg/kg/dose once daily or every other day
Adult: 250–375 mg/dose once daily or every other day

Glaucoma
Child:
PO: 8–30 mg/kg/24 hr ÷ Q6–8 hr
IM/IV: 20–40 mg/kg/24 hr ÷ Q6 hr
Adult:
PO (simple chronic open angle): 1000 mg/24 hr ÷ Q6 hr


Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS
CURRENT LABELING
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
NEW LABELING
(effective June 30, 2015)
8.1 Pregnancy
includes Labor and Delivery
8.2 Lactation
includes Nursing Mothers
NEW
8.3 Females and Males of Reproductive Potential

Children are not Little Adults!

- Different & Unique Exposures @ a critical period
- Dynamic Developmental Physiology

Pharmacokinetic Consideration :Absorption

GI absorption of drugs

- PH dependent passive diffusion : changes in PH in term and preterm infants
- Gastric emptying time: delayed in premature infants

Risks of oral drugs on immature GI

Pharmacokinetic Consideration : Absorption

Intramuscular

- Small muscle mass
- Decreased perfusion
- Vasomotor instability
- Decrease muscle contraction
- Volume limitation
- Rarely in neonates

Pharmacokinetic Consideration :Absorption

Transdermal

- Underdeveloped epidermal barrier
- High surface area to body mass
- Absorption from the skin is markedly higher in children
- Predisposes them to toxicity

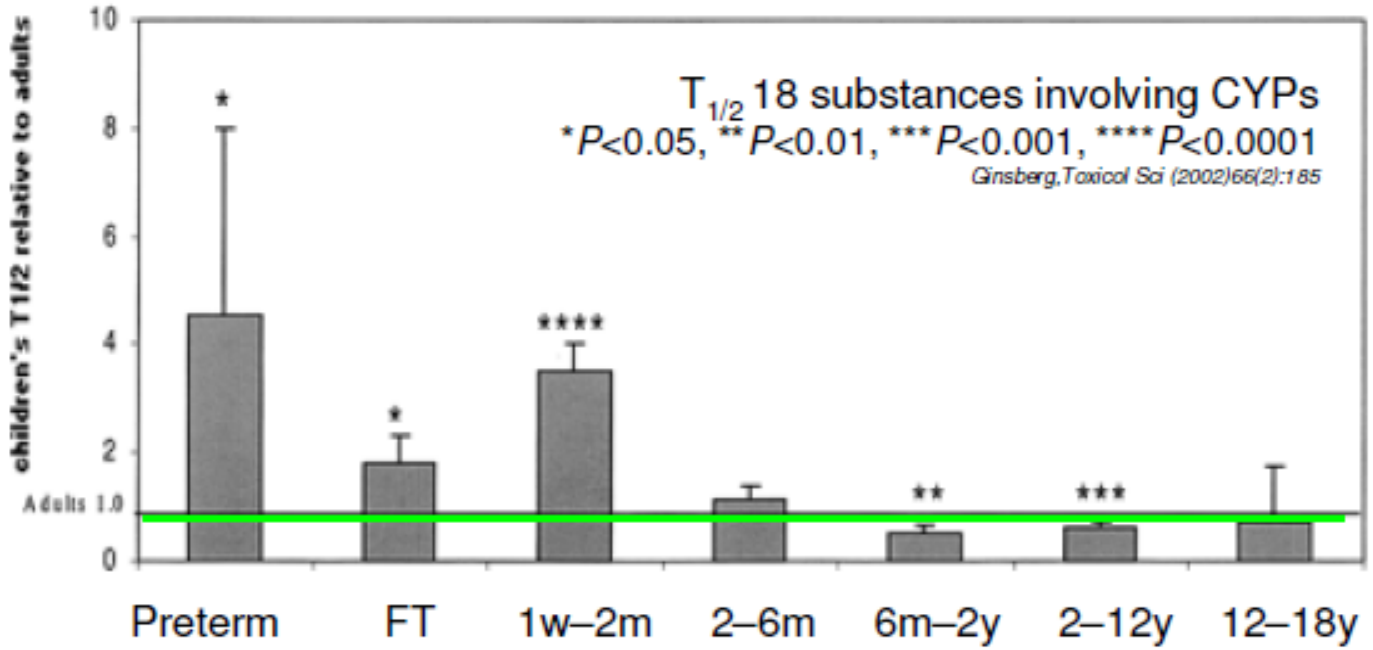
Pharmacokinetic Consideration: Distribution

Distribution of any drug in the body is determined by its properties and the physiological properties of the patient

- Total body water (85% in neonates vs 60% in adults)
- Extracellular water (50%in neonates vs 19% in adults)
- Protein binding (decreased binding in neonates due to decreased proteins,, decrease binding capacity and affinity to drugs , competition on binding) increase free drug (Sulpha)
- Lipid solubility affect distribution and toxicity (brain and breast feeding)

Pharmacokinetic Consideration :Metabolism

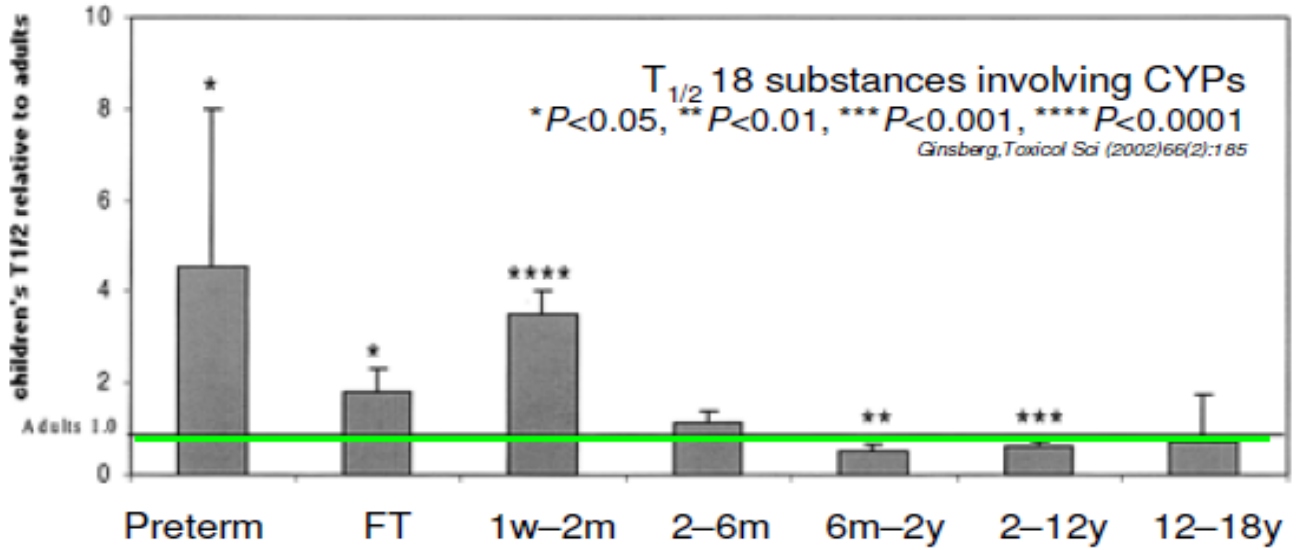
- Immature metabolism pathways
- Increased toxicity : Gray baby syndrome
- Decreased effect and need for higher doses : morphine in premature infants



- More differences for substances predominantly metabolized by P450 enzymes in liver

Pharmacokinetic Consideration : Elimination

- **Slower**



- More differences for substances predominantly metabolized by P450 enzymes in liver

Efficacy

Different pathogenesis of the same disease: different disease ??

Asthma

1- Adults: non specific airway hyperirritability

2- children: Atopic : adjunctive therapy with antihistamine /hypo sensitization

Higher doses of some drugs in children : digoxin (less receptors affinity in myocardium , more binding to erythrocytes)

Obese children might need higher doses

Toxicity

- Propylene glycol used as stabilizer in many injectable drugs can cause hyperosmolarity in infants
- Ethanol is a solvent for many oral drugs: safety is not established (oral dexamethasone)
- Common cold medicines (antihistamine, decongestants, antitussives, expectorants)AAP > 2 years , manufactures >4 years
- Tetracycline : staining of teeth

Drug Administration issues

- Iv line and compatibility
- Need for infusion pumps , connection tubes volume
- Altering the dosage forms : stability , concentration issues , volume issues , decreased efficacy, side effects (Creon)

Drug Administration issues

- Medication adherence and tolerance, relation between dose and feeding , number of doses, palatability, trick to deliver the drug(thyroxine)
- Forms of drugs available : tabs versus solution
- Tabs > 12 year

How to Prescribe a Drug for a Child /The Process

Right Diagnosis:

Wheezy chest in a 2 year old

1-Asthma

2-Bronchiolitis

3-Forighn body aspiration

4- GERD

How to Prescribe a Drug for a Child /The Process

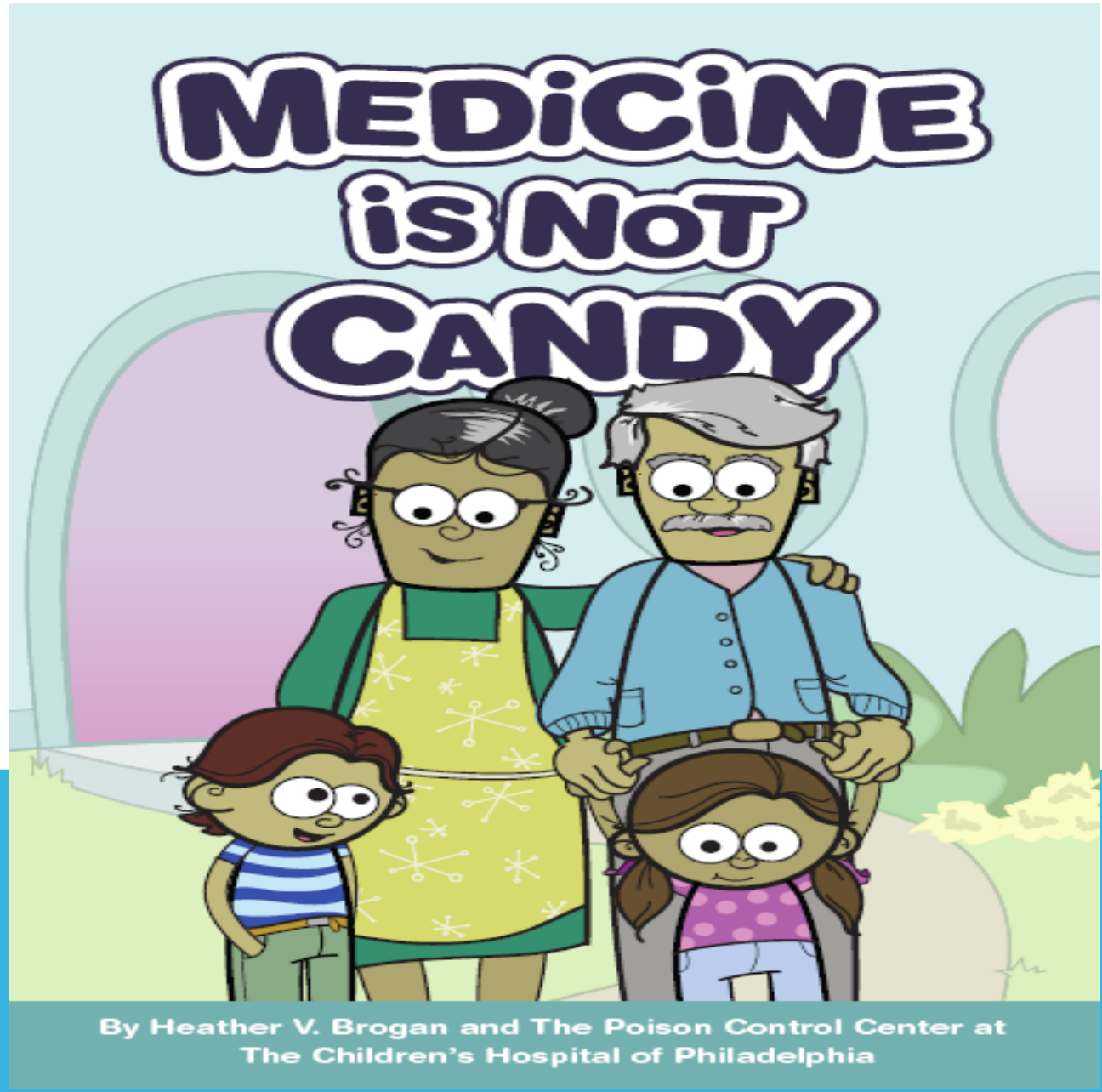
- Decide the best treatment :
  - Asthma : Bronchodilators
  - Bronchiolitis: HTS neb
  - Foreign body aspiration: bronchoscopy
  - GERD: Antireflux

- Role out contraindication
- Check liver and kidney
- Check comorbidity
- Allergy

How to Prescribe a Drug for a Child /The Process

- Interaction with co administered drugs /complementary food
- Calculate the dose /kg/BSA)
- Determine duration
- Talk to parents (previous experience, tolerance issues , tricks , explain side effects ,storage conditions)
- Plan for follow up improvement, side effects ,levels

THANK YOU !


MEDICINE
IS NOT
CANDY
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