**Clinical Pharmacokinetics**

**Pharmacokinetics of drug disposition during pregnancy and lactation**

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Educational Objectives:

1. Describe the physiologic changes that occur during pregnancy that may alter the pharmacokinetics of medications in pregnancy.

2. Given the characteristics of a medication, estimate the potential impact of pregnancy on the drug’s Vd, metabolism, clearance and clinical effect.

3. Given a medication for which information is available regarding its disposition during pregnancy, recommend how the drug should be monitored and dosed.

4. Given the characteristics of a new medication, determine the safety of using that new drug in humans during breastfeeding.

**FYI:**

* 1st Trimester: Weeks 0-13
* 2nd Trimester: Weeks 14-27
* 3rd Trimester: Weeks 28-delivery

I. Pharmacokinetic data in pregnancy

A. The challenge

B. Therapeutic goals

**Fetus**

Limit drug exposure

Fetal Therapy

**Mother**

Insure Efficacy

Limited Toxicity

**Mother**

Insure Efficacy

Limited Toxicity

**Mother**

Insure Efficacy

Limited Toxicity

**Mother**

Insure Efficacy

Limited Toxicity

II. Physiochemical properties affecting drug transport across the placenta and into breast milk

A. Molecular Weight

*Low molecular weight < 500 daltons can pass into placenta*

B. Protein Binding

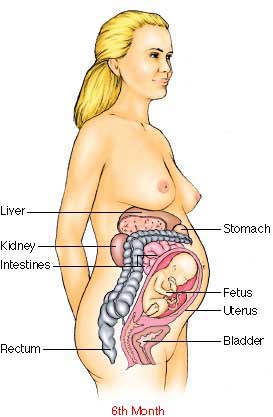
*Low protein binding can pass into placenta*

C. Lipid Solubility

*High lipid can pass into placenta*

D. pKa

1. Ion-trapping: *fetal pH is slightly acidic. Basic drug goes into fetus and ionizes (stays in fetus)*
2. Non-ionized can pass into placenta

III. Drug disposition during pregnancy

A. Physiologic changes that occur during pregnancy

Decrease gastric motility

Increase in pH (basic)

Increase cardiac output

Increase hepatic flow

Increase renal blood flow

Increase body water = diluted albumin

B. Gastrointestinal absorption

1. Physiologic Changes/pharmacokinetic effects

a. *Decreased intestinal motility (Prolonged GI Transit Time)*

*b. Increased gastric pH*

2. Clinical Relevance

1. *Decrease motility = decrease absorption*

C. Distribution

1. Physiologic changes/pharmacokinetic Effects

a. Increased total body water leading to ↑ Vd. Delay in effect

b. Changes in protein binding: Albumin begins to decline in the second trimester leading to ↑ fraction unbound

2. Clinical Relevance

1. Decrease in Cpk/Cmax in drugs with small Vd
2. Most drugs no change in Css

**EXCEPT:**

1. Low extraction ratio drugs that are highly protein bound where total plasma concentration is monitored

Examples:

* Valproic acid/phenytoin

**Total serum concentration decreases by 50%, but unbound**

**Serum concentration is unchanged (unbound is what matters).** **What do you think may happen in clinical practice when total serum concentration is usually monitored?**

* **Effect on the patient?**
* *CL hepatic = fu \* CL intrinsic*
* *Css (total) = dose/fu\*Cl intrinsic (if fu increase, Css total decrease)*
* *Css(free) = fu \* (Css total) (if fu increase and Css total decrease then Css free stays the same)*
* **Response of the physician interpreting the total concentration?**

*Don’t change dose. Free concentration wouldn’t change*

1. High extraction ratio drugs administered IV (e.g. fentanyl,midazolam)

CL hepatic = LBF (liver blood flow)

C total (same) = dose/LBF

C free (increase) = fu \* C total

**Flashback from PY2 PK**

Glossary:

ClH- hepatic clearance

fu= fraction unbound

Clint = intrinsic clearance

LBF= liver blood flow

Css= steady state concentrations

* Extraction ratio (ERH): % or ratio of drug removed after 1st pass through the liver
* Low extraction ratio

Css(total) = Dose/fu x Cl int and Css(free) = fu x Css(total)

* High extraction ratio

Css(total) = Dose/LBF, Css(free)= fu x Css(total)

D. Metabolism

1. Physiologic changes/Pharmacokinetic effects

a. Hepatic blood flow is increased during pregnancy

* High ERH  drug clearance is dependent on liver blood flow

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TP question: NP is a 28 y/o female, 29 weeks pregnant that comes into her OB office with complaints of severe headache. She was recently started on metoprolol for pregnancy induced hypertension. (Metoprolol- PK: large Vd, low protein binding, high ERH, minimal renal clearance)

BP: 155/95

What pharmacokinetic changes would you expect to occur and dose adjustment required when using metoprolol in this patient?

1. Decreased hepatic clearance which would need a ↓ dose
2. Increased hepatic clearance which would need an ↑ dose
3. Increased clearance but no dose adjustment is needed

b. The activity of some enzymes is increased and others are decreased.

* Genetics my take precedent over changes that usually occur in pregnancy. Low metabolizes often do not experience a further decline in enzyme activity during pregnancy.
* The effect on elimination rate for medications metabolized by multiple enzymes is difficult to predict.

* Changes in enzyme activity during pregnancy

**Enzymes with Increased Activity During Pregnancy**

*4:30 Don’t memorize*

|  |  |  |
| --- | --- | --- |
| **Enzyme** | **Substrate** | **Predicted Clinical Effect** |
| CYP2A6 | Nicotine | May need higher doses of nicotine replacement therapy |
| CYP2C9 | Phenytoin (CYP2C19 is a minor metabolic pathway) | Monitor free levels. Doses often need to be increased in third trimester |
| CYP2D6 | Fluoxetine | Increased clearance most data in third trimester |
| CYP3A4 | Carbamazepine | Difficult to predict due to decrease in protein binding |
|  | Protease inhibitors (indinavir, lopinavir, ritonavir, saquinavir) |  |
|  | Theophylline | Also metabolized by CYP1A2, usually no change in serum concentration |
|  | Nifedipine | Increased clearance |
| UGT1A4 | Lamotrigine | Increased clearance as early as the first trimester. Most significant in patients on monotherapy |
| UGT2B7 | Morphine | Increased clearance |
|  | Zidovudine | Variable |

**Enzymes with Decreased Activity During Pregnancy**

|  |  |  |
| --- | --- | --- |
| **Enzyme** | **Substrate** | **Predicted Clinical Effect** |
| CYP1A2 | Theophylline | Offset by increased activity of CYP3A4 |
| CYP2C19 | Phenytoin | Minor pathway in non-pregnant women |

E. Renal Clearance

1. Physiologic effect/ Pharmacokinetic effect

a. Increased renal blood flow/ ↑ glomerular filtration rate (GFR)

2. Clinical Effect

1. Decreased efficacy of drugs with primarily renal elimination
   * 1. Examples: Lithium, beta-lactam antibiotics, aminoglycosides, etc.

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TP question: JS is a 32 y/o female, 6 weeks pregnant, that is scheduled to you see you in anticoagulation clinic.

Wt: 62 Kg

Allergies: None

PMH: Protein C deficiency,

TIA (2 years ago)

Meds: Warfarin (D/cd 4 weeks ago)

Enoxaparin 60 mg SC Q12 hrs

Enoxaparin PK: Small Vd, low PB, primarily renally cleared

What would be the best plan to manage JS’ anticoagulation?

1. Order a Xa level and adjust dose based on results
2. Increase dose to 80 mg SC q12 hr
3. Increase dose to 60 mg every 8 hrs
4. Do nothing and monitor for signs of thrombosis

IV. Post-partum

1. Reassess and adjust doses in the postpartum period as drug distribution/metabolism/clearance will change

V. Drugs in Breast Milk

1. How drugs get into breast milk

1. Passive diffusion: Movement from High to low concentration drugs

2. Active Transport

1. Infant Exposure
2. Drug Concentration in Milk
3. Bioavailability of Drug in the Infant
4. Calculating the Infant Dose/Exposure
5. M/P ratio

M/P ratio: milk to plasma ratio = Milk concentration/Plasma concentration

Higher the ratio: the more drug in milk 🡪 transfer to baby

1. Absolute Infant Dose (D inf)

Absolute infant Dose = [milk] \* Volume of milk

Dinf (mg/kg/day)= Drug Concentration in milk (Cmax or Cav) X volume of milk

Drug conc= average maternal conc x M/P

Usual volume of milk = 0.15L/kg

ingested

1. Relative Infant Dose (RID)

RID (%) = [Dinf (mg/kg/day)/maternal dose (mg/kg/day)] X 100

a. < 10% acceptable

b. 10-25% use with caution

c. > 25% avoid use unless necessary

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A woman is started on a medication to treat postpartum depression. The drug is lipophilic and is 40% protein bound. Based on these characteristics, would this drug cross into breast milk?

1. Yes
2. No
3. Can’t make a guess based on the information provided.

**Will not be tested on:**

TP question

A 20 year old mother gave birth to a full-term infant by C-section 24 hours ago. She is currently breastfeeding but is also in a lot of pain and the MD orders oxycodone 5 mg every 4hours prn. use oxycodone for pain?

Why or why not? If not, what else would you recommend?

TP question

A patient (postpartum and currently breastfeeding her 4 month-old) comes into your pharmacy with an Rx for an antibiotic for mastitis. The dosage is 300 mg four times/day, the drug’s average milk concentration is 3.3 mg/L. The mom weighs 60kg. What is the RID of maternal dose that infant would receive? Infant is 8 kg.

Would you recommend another antibiotic?

Resources for drugs in breast milk:

1. LactMed <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

2. Hale , T.W. Medications and Mothers' Milk: A Manual of Lactation Pharmacology. 14th ed. Hale Pub. ( 2010)

3. www.kellymom.com