

20th ANNUAL HIV CONFERENCE
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AIDS Education and Training Center

May 13-14, 2011
Orlando, FL

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Pharmacokinetic Variability and Drug Interactions: Pediatric Focus

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Lecture Objectives

- **Upon completion of this lecture, the participant should be able to:**
 - Discuss why pharmacokinetic and pharmacogenomic concepts should be considered when implementing drug regimens for children
 - Identify gaps in our understanding of pharmacokinetic variability and the areas in need of further research
 - Understand the role of pharmacokinetic variability when evaluating drug interactions with antiretrovirals



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Review of Basic Concepts

- **Pharmacokinetics**
 - Definition: The study of the process by which drugs are absorbed, distributed, metabolized and excreted from the body
- **Pharmacodynamics**
 - Definition: quantification of the relationship between drug concentration and clinical endpoints or effects, desired or undesired



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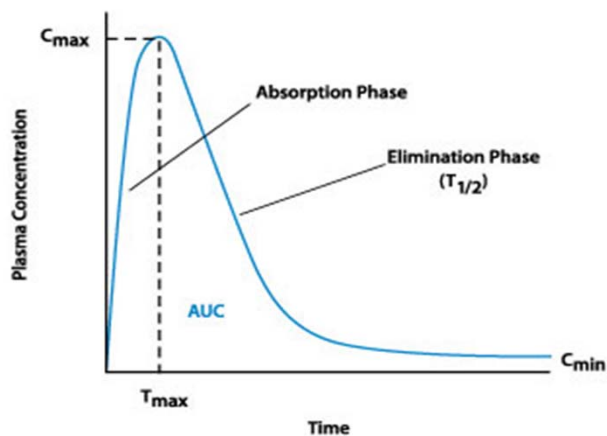
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Review of Basic Concepts

- **Pharmacogenomics**
 - Definition: The study of the interaction between genetic polymorphisms and drug pharmacokinetics or pharmacodynamics
- **Area Under the Curve (AUC)**
 - Important for understanding biopharmaceutics and pharmacokinetics
 - Definition and clinical significance when interpreting overall drug exposure for drug interactions

Understanding Area Under the Curve



Basic Pharmacokinetic Considerations for Drug Regimens in Pediatric Cases

- Inadequate drug exposure will result in treatment failures
- Dosing must account for rapid growth, drug interactions
- Children consistently require higher weight-based dosing of ARV meds because of:
 - Differences in body composition
 - Metabolic activity
 - Absorption



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Pharmacokinetic Considerations

- ABSORPTION
- VOLUME OF DISTRIBUTION
- METABOLISM
- ELIMINATION



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Considerations in Oral Absorption

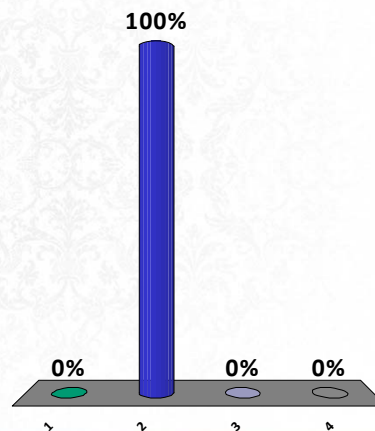
- **Effect of Age**
 - Oral absorption reduced in premature infants and neonates due to:
 - Differences in gastric acid secretion
 - Differences in pancreatic and biliary function
 - Gastric acid output per kilogram is lower in premature infants and increases with age to adult levels by 6 months
 - Significance: Low gastric acid secretion can result in increased serum concentrations of weak bases and acid labile medications (eg penicillins) and decreased serum concentrations of weak acids (eg phenobarbital)

Considerations in Oral Absorption

- **Changes in pancreatic and biliary function**
 - 50% less secretion of amylase and lipase than adults and reach adult values as early as the end of the first year and as late as 5 years of age
 - Deficiency in pancreatic secretions and bile salts results in decreased bioavailability of prodrug esters such as erythromycin
- ***Limited data on oral bioavailability of medications in infants and children***

Why is it important to understand what is meant by AUC when interpreting drug interaction data?

1. Indicates maximum serum concentration the drug
2. Indicates minimum serum concentration of the drug
3. It provides indication of total drug exposure
4. Indicates extent of drug excretion



Considerations for Volume of Distribution

- Extracellular fluid and total body water per kilogram of body weight are increased in neonates and infants resulting of higher values for water soluble drugs and decreases with age
- Age dependent changes in body composition of water alter the physiologic spaces where drugs are distributed
 - Example: Total Body Water (TBW) decreases from 85% in premature infants, 75% in full term infants and to 60% in adults
 - Extracellular water falls from 45% in infants to 25% in adults
- Neonates and infants have lower serum albumins and this may affect highly protein bound drugs

Considerations for Drug Metabolism

- Drugs are metabolized mainly in the liver via the cytochrome P450 system.
- There are 3 families of enzyme systems in this family consisting of CYP1, CYP2 and CYP 3
- More than 50% of biotransformation of drugs occur with the CYP3 system with the majority of these being CYP3A4



Examples of Drugs Metabolized by Various Enzyme Systems

- **Protease Inhibitors**
 - All PIs are metabolized via CYP 450 (primarily via 3A4 isoenzyme)
 - Ritonavir & most PIs – 3A4 substrate & inhibitor
 - May induce CYP1A2 and CYP2C9, 2C19, 1A2, 2E1 as well
 - Tipranavir – 3A4 inducer, but TPV/r – inhibitor



Examples of Drugs Metabolized by Various Enzyme Systems

- **NNRTIs**
 - Efavirenz – mixed 3A4 inducer and inhibitor
 - Nevirapine – inducer
 - Etravirine - 3A4 substrate and inhibitor, also 2C9 and 2C19 substrate and inhibitor
 - Delavirdine - inhibitor



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Considerations for Drug Metabolism

- **Metabolism slower at birth**
- **Certain enzymes of oxidation are not fully developed until later in childhood or adolescence**
- **Cytochrome P450 isoenzymes (CYP2C9, CYP1A2) and other enzyme systems develop at various ages, ranging from a few months to 3 years of age (glucuronidation varies greatly) , with delayed development in premature infants**
- **Neonates have 28% of adult CYP4 activity at birth**



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Considerations for Drug Metabolism and Excretion

- Reduced dosing of medications undergoing hepatic metabolism may be required for full term and premature neonates
- Hepatic enzyme activity increases to nearly twice as much as adults at 6 months of age and may continue to be high through puberty, around 9 to 12 years of age and higher doses may be required. Examples include various anticonvulsants (eg phenytoin, valproic acid)



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Considerations for Elimination

- Renal drug clearance is reduced in infants due to immature renal function
- Glomerular Filtration Rate (GFR) increases rapidly during first two weeks of life and continues to reach adult clearance levels by 8 months to 12 months
- Dosages should be reviewed and adjusted accordingly



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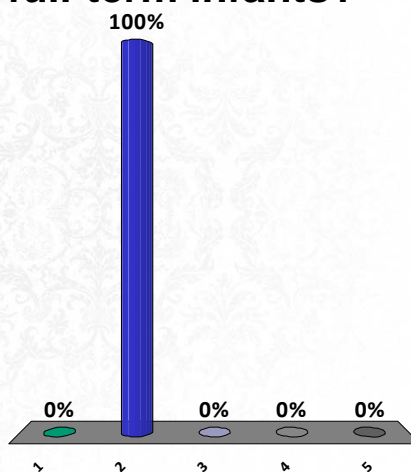
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Other Considerations

- **Role of drug transporters?**
 - p-glycoprotein transporters may have important role in absorption, distribution and clearance of PIs and NNRTIs but has been poorly studied
- **Activity of drug transporters such as p-glycoprotein has not been sufficiently delineated**
- **May vary in patients due to genetics**

What percentage of body weight represents total body water in full-term infants?

1. 50%
2. 75%
3. 85%
4. 60%
5. None of the above



Understanding Pharmacokinetics and Drug Interactions of ARVs: Focus on Pediatrics

- The majority of studies concerning the pharmacokinetics of antiretrovirals have been in adults
- Understanding how pediatric patients differ with respect to key pharmacokinetic factors is important when designing a therapeutic regimen

ART Options

- NRTIs (Nucleoside OR Nucleotide Reverse Transcriptase Inhibitors, aka “Nukes”)
- NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors, aka “Non-Nukes”)
- PIs (Protease Inhibitors)
- Fusion
- Entry Inhibitors
- Integrase Inhibitors



Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI's)

- Zidovudine (AZT, ZDV, Retrovir) – 3/1987
- Didanosine (ddI, Videx[®], Videx EC[®]) – 10/1991
- Stavudine (d4T, Zerit[®]) – 6/1994
- Lamivudine (3TC, Epivir[®]) – 11/1995
- Abacavir (ABC, Ziagen[®]) – 12/1998
- Tenofovir (TDF, Viread[®]) – 10/2001
- Emtricitabine (FTC, Emtriva[®]) – 7/2003



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NRTI Combinations

- **Combivir[®] (AZT, 3TC) – 9/1997**
- **Trizivir[®] (AZT,3TC,ABC) – 11/2000**
- **Epzicom[®] (ABC,TDF) – 8/2004**
- **Truvada[®] (FTC,TDF) – 8/2004**



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Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's)

| Agent | Approved |
|----------------------------------|----------|
| • Nevirapine (NVP, Viramune®) | 6/96 |
| • Delavirdine (DLV, Rescriptor®) | 4/97 |
| • Efavirenz (EFV, Sustiva®) | 9/98 |
| • Etravirine (ETR, Intelence®) | 1/08 |



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Protease Inhibitors (PI's)

| Agent | Approved |
|----------------------------------------|----------|
| • Saquinavir-HGC (SQV-HGC, Invirase®) | 12/95 |
| • Ritonavir (RTV, Norvir®) | 3/96 |
| • Indinavir (IDV, Crixivan®) | 3/96 |
| • Nelfinavir (NFV, Viracept®) | 3/97 |
| • Saquinavir-SGC (SQV-SGC, Fortovase®) | 11/97 |
| • Amprenavir (APV, Agenerase®) | 4/99 |
| • Lopinavir/ritonavir (KAL, Kaletra®) | 9/00 |
| • Atazanavir (ATV, Reyataz®) | 6/03 |
| • Fosamprenavir (fos-APV, Lexiva®) | 10/03 |
| • Tipranavir (TPV, Aptivus®) | 6/05 |
| • Darunavir (DRV, Prezista®) | 6/06 |




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Fusion and Entry Inhibitors

| Agent | Approved Fusion |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| <ul style="list-style-type: none"> • Enfuvirtide (T-20, Fuzeon®) Entry Inhibitor (CCR5 Inhibitor) • Maraviroc (Selzentry®) <p>Not approved for children under 16 yrs</p> | <p>3/03</p> <p>8/07</p> |



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Integrase Inhibitor

- **Raltegravir (Isentress®)**
 - Introduced October 2007
 - New class used in treatment experienced patients
 - Use in adolescents 16 years and older
 - Used in patients with multiply-resistance strains of HIV
 - Inhibition of integrase prevents insertion of HIV DNA into the human DNA genome, thus blocking the ability of HIV to replicate



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Case Analysis

- RL is a 16 year old female (120 lbs) infected with HIV. Currently, she is seen in the clinic with her mother who also is HIV positive who is currently on ARV therapy as well. There has been full disclosure for 4 years and the patient has received education concerning the importance of taking responsibility for her own therapy and the importance of adherence to therapy.
- Allergies: penicillins and cephalosporins



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Case Analysis continued

- **Current medications at today's visit include the following:**
 - Combivir® (Lamivudine/zidovudine) 1 tablet po bid
 - Atazanavir 300mg po once daily
 - Ritonavir 100mg po once daily
 - Ciprofloxacin 500mg po bid (completing UTI therapy)
 - Alka-Seltzer Effervescent Tablets prn headache
 - Tums prn upset stomach



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Question

- **What counseling tips would you give this patient?**
 - GROUP DISCUSSION

Pharmacokinetic Considerations: NRTIs

- **NRTIs are not affected by cytochrome P450 hepatic enzyme system**
- **Drug interactions with NRTIs are involved more with:**
 - Overlapping adverse effects
 - Competition for renal elimination
 - Oral absorption
 - Unexplained alterations in clearance

Drug Interactions: NRTIs

- **Abacavir**
 - Not metabolized by cytochrome P450
 - Metabolized by alcohol dehydrogenase and alcohol increases levels by 41%
- **Didanosine**
 - Didanosine and tenofovir considerations
 - Effect of pH (suspension) on absorption of other medications
 - Overlapping toxicities (e.g. pancreatitis, peripheral neuropathy)
 - Drugs that decrease renal function can decrease ddl clearance



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Drug Interactions NRTIs

- **Emtricitibine**
 - Avoid concurrent use with lamivudine due to similar resistance profiles
 - Competes for tubular secretion and drugs that reduce renal clearance may also reduce clearance of emtricitibine
- **Lamivudine**
 - Same as above



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Drug Interactions NRTIs

- **Stavudine**
 - Do not use with zidovudine due to virologic antagonism
 - Overlapping toxicity with ddl
 - Drugs that decrease renal function could reduce clearance of stavudine



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Drug Interactions NRTIs

- **Zidovudine**
 - Interacts with drugs that cause bone marrow suppression (additive effects). Examples: ganciclovir, ribavirin etc.
 - Stavudine: viral antagonism
- **Tenofovir**
 - Drugs that decrease renal function or compete for active tubular secretion could reduce clearance
 - Didanosine levels increased when given together
 - Tenofovir can reduce atazanavir concentrations
 - Atazanavir and lopinavir/ritonavir can increase levels of tenofovir and potentiate toxicity



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Drug Interactions NNRTIs

- **Efavirenz**
 - Mixed inducer/inhibitor of cytochrome P450 3A4 and can be involved with many potential agents
 - Remember: effects on inducing and inhibiting enzymes!!
 - Dosages of concurrent medications may need to be adjusted to maintain appropriate concentrations
- **Nevirapine – inducer**
 - Auto-induction occurs in 2 to 4 weeks
 - Do not administer with atazanavir (boosted or not)
- **Etravirine**
 - 3A4 inducer and substrate
 - Also, 2C9 and 2C19 substrate and inhibitor; inhibitor of P-glycoprotein



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Drug Interactions NNRTI

- **Etravirine continued**
 - Avoid the following:
 - Tipranivir/ritonavir, fosamprenavir/ritonavir, ritonavir, unboosted PIs



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Examples of Potential Medications that May Interact

- **Anticonvulsants**
 - Serum levels of anticonvulsants may decrease
 - Levels of NNRTI may decrease as well
- **Rifampin**
 - Efavirenz levels decreased (AUC decreased by 26%)
 - Not recommended with etravirine or nevirapine
- **Other medications.....**

Protease Inhibitor Drug Interactions

- **Major emphasis for drug interactions with PIs center on hepatic metabolism**
- **Major enzyme system affected is 3A4 but can affect other systems as well**
 - **EXAMPLES**
- **Ritonavir is the most potent inhibitor of 3A4 and an entire host of therapeutic agents are affected**

Major Class Examples of Interactions with Protease Inhibitors

- **Antacids**
 - Atazanavir
 - Fosamprenavir
 - Tipranavir/ritonavir
 - Dosing Recommendations to avoid reduced absorption with antacids for each agent



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Protease Inhibitor Drug Interactions

- **Other acid-suppressing agents**
 - H₂ receptor antagonists (eg famotidine) with atazanavir and fosamprenavir – dosing recommendations
 - Use of Proton Pump Inhibitors with atazanavir and other PIs



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Protease Inhibitor Drug Interactions

- **Anticonvulsants**
 - Carbamazepine –
 - levels of atazanavir and fosamprenavir can become reduced if not boosted with ritonavir
 - If boosted, carbamazepine levels may increase
 - Monitor serum concentrations to avoid anticonvulsant toxicity
 - Lamotrigine –
 - AUC decreased by 50% in patients on LPV/r

Protease Inhibitor Drug Interactions

- **Anticonvulsants continued**
 - Phenobarbital – potent enzyme inducer
 - Phenytoin – serum concentrations can become reduced depending upon combination of ARVs used. AUC may be reduced by as much as 30%
 - Valproic acid – LPV/r levels increase by as much as 75%
- **Considerations for managing interactions with anticonvulsants**

Protease Inhibitor Drug Interactions

- **Tricyclic Antidepressants**
 - All ritonavir boosted PIs can lead to increased levels of antidepressants. Begin therapy with lowest dosage
- **Rifampin**
 - Reduces PI levels even if boosted
- **Rifabutin AUC may increase depending upon combination of PIs**

Protease Inhibitor Drug Interactions

- **Other Interactions and Mechanisms to Consider**
 - Fluticasone and boosted PIs
 - Antifungal agents
 - Benzodiazepenes
 - Herbal Preparations
 - St John's Wort
 - Kava Kava
 - Others

Other Interactions: Raltegravir and Maraviroc

- **Raltegravir**
 - Rifampin
 - Omeprazole
- **Maraviroc**
 - Concomitant use with other ARVs depending upon enzyme inhibition
 - Anticonvulsants
 - Antifungal
 - Rifampin/Rifabutin



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Therapeutic Drug Monitoring?

- **Therapeutic Drug Monitoring**
 - Definition
 - When is it useful in practice?
 - What are the problems associated with its interpretation and use in clinical practice?



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Summary

- **Pediatric population is prone to potential problems with drug disposition and interactions because:**
 - Physiologic and pharmacokinetic variability can be significant as compared to adults
 - As children transition to assume responsibility of their care, continuous education is important with regard to interaction potential between other prescription and nonprescription meds
 - Use appropriate literature sources to evaluate regimens to avoid and assist in managing drug interactions

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