Clinical Nephro-Pharmacology in Children with Renal Diseases – what should we know?
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Disclosures

• I have no financial relationships to disclose relevant to my presentation
Objectives

At the end of the session, you will be able to:

- Understand developmental changes of drug disposition in children;
- Understand the particular role of the kidney;
Which statement is correct?

1. Most drugs are cleared by glomerular filtration
2. Only a small number of drugs are cleared by the kidneys
3. Most drugs are cleared by tubular secretion, for instance, through organic anion transporters
4. In the first year of life, you can dose Gentamycin once daily
Basic Principles of Drug Clearance
How drugs are cleared

• Oral drugs
  – Gastrointestinal Fate/Bioavailability
  – Pharmacokinetics
  – Volume of Distribution
  – Plasma Protein Binding
  – Elimination

• Intravenous Drugs
  – Bioavailability = 1
Bioavailability

• Oral bioavailability
  – ratio of the Area Under the (Time Concentration) Curve (AUC) of the extra venous drug divided by the AUC of the intravenous dose
  – Often doses are different for iv vs. oral

\[
F = \frac{AUC \ (extravenous) \times Dose \ (iv)}{AUC \ (iv) \times Dose \ (extravenous)}
\]
Relative Bioavailability

• Occasionally, the data on IV dosing are not available
• Clearance (CL) and volume of distribution (Vd) cannot be determined
• Parameters from oral data are defined as apparent parameters, namely CL/F and Vd/F.
• Often, the bioavailability is < 1.
Pharmacokinetics – how to get to dosing

Drug Dosing

- Peak
- Unacceptable Toxicity
- Therapeutic Window
- Trough
- IC 50
- Poor Activity
- C_{Max}
- C_{Min}
- Time after taking Drug
Volume of Distribution

- Drugs rarely stay confined in the circulating blood pool
  - Example inulin
- Drug diffuses into tissues, organs and other fluid spaces
- Samples for measurement can usually only be collected in plasma or blood
- It is useful to relate the concentration to a total amount of drug in the body.
Volume of Distribution

- $V_d$ is a proportionality constant that relates the drug concentration in the blood to the total amount of drug in the body.

- Assuming that $A$ is the total amount of the drug in the body and $C_p$ is the plasma concentration, the volume of distribution can be calculated using the following formula:

$$V_d = \frac{A}{C_p}$$

- This is used to calculate the clinical loading dose as follows:

$$Loading \ dose = C_p\text{-desired} \times V_d$$
Basic 3-compartmental model

Oral Dose → Oral Absorption Rate → Central Compartment \( V_C \)

Intravenous Drug Input → \( K_{12} \)

Metabolic Clearance → \( K_{31} \)

Renal Clearance

Absorption Compartment

Central Compartment \( V_C \)

Peripheral Compartment \( V_2 \)

Peripheral Compartment \( V_3 \)
Volume of Distribution

• The volume of distribution (per kg body weight or body surface area) also changes significantly as a child grows, especially in the first 2 years of life.

• The proportion of total body water in a term newborn is approximately 75-80%, which decreases to approx. 60% at the age of 5 months.

• Extracellular water also decreases, from approx. 37% in a newborn to less than 20% in an adult.
Clearance

• Clearance ($CL$) is a measure of drug elimination.
• It represents the volume of blood (or plasma) from which a drug is completely removed per unit of time.
Clearance

• The liver and the kidney are the two most important organs responsible for drug elimination.
• The liver (though not exclusively) metabolizes drugs and can excrete them through bile.
• The kidney filters and excretes drugs and metabolites.
• Other tissues may also significantly contribute to a drug’s clearance.
• Therefore, overall $CL$ can be separated into individual components and is expressed as:

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{other}$$
Hepatic Clearance

- Drug metabolism primarily occurs in the liver.
- The biotransformation of the drug is influenced by its structural and chemical properties, which in turn influences its affinity for transporter proteins and various drug-metabolizing enzymes.
- Hepatic blood flow and plasma protein binding may also affect biotransformation.
- Drugs with a high affinity for metabolizing enzymes are exceptionally influenced by changes in hepatic blood flow.
- Particularly marked variability exists for the CYP3A4, CYP1A2, CYP2D6, and UGT2B7 enzymes.
Hepatic Clearance

- Beyond drug metabolism, recent studies have highlighted the importance of **uptake and efflux drug transporters** in mediating the drug disposition.
- Several uptake **transporters** on the **sinusoidal membrane** of the hepatocyte mediate the uptake of drugs from the blood into the hepatocyte.
- Canalicular ATP-binding cassette (ABC) efflux transporters may pump drugs found in the hepatocyte into the bile, a process that mediates the **biliary clearance** of drugs.
- Drug transporters: organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, multi-drug resistance associated protein 2 (MRP2), and **P-glycoprotein**
Important role of the kidney
Renal Clearance

- Many drugs are excreted through the urine (61%).
- This occurs primarily through the active secretion of acids and bases (mainly in the proximal tubule), and to a lesser extent through glomerular filtration.
- Cationic drugs are secreted into the urine through two main transporter molecules, human organic cation transporters (OCTs) and multidrug and toxin extrusion proteins (MATEs).
- Less is known about the anion transporter molecules and many have not yet been identified. Organic Anion Transporters (OATs) are remarkable for their broad substrate specificity and their ability to exchange extracellular against intracellular organic anions.
Renal Clearance

• Several classes of drugs interact with human OAT1, OAT2 and OAT3, including angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor antagonists, diuretics, and others.

• Reabsorption of the drug along the proximal and distal tubules and the collecting duct mitigate the drug’s elimination from the body both by filtration and by active secretion.

• Although reabsorption is primarily a passive process, it can have a profound impact.

• Small, non-polar drugs are carried with the water that is filtered through the kidneys, the majority of which is reabsorbed, providing an avenue for their reabsorption.
Renal Clearance

• Furthermore, drugs with pK_a values that fall within the range of urinary pH (5.0–8.0) may be profoundly affected by changes in urinary pH.

• Serial blood and urine samples are used to calculate renal clearance, which is calculated by dividing the renal excretion rate by the average plasma concentration.
Plasma Protein Binding

• Plasma protein binding is crucial for glomerular filtration and for the ability of renal replacement therapy to clear drugs.
• It reduces the amount of drug that can be filtered, but does not usually alter the rate at which charged organic molecules are secreted through the proximal tubule.
Plasma Protein Binding

• The type of renal replacement therapy is important to consider. If conventional hemodialysis is employed with mostly diffusive clearance, the removal of renally-excreted drugs such as vancomycin is usually negligible.

• Newer high-flux membranes with more permeable dialyzer membranes and additional convective clearance may, however, result in a significant decrease in the patient’s vancomycin concentration.
Vancomycin and Aminoglycosides

- Nephron endowment may be more important than GFR in the tubular secretion of vancomycin and aminoglycosides.
- Allegaert conducted an elegant study to demonstrate this concept. 1212 drug measurements (vancomycin, aminoglycosides) were made in 531 subjects, and postmenstrual age (PMA) was found to be more important in predicting drug clearance than renal function. (There was a 25.2% prediction of variability by PMA versus 3.5% by GFR).
Saturable Elimination

• $CL$ is not always independent of drug concentration, especially if an excessive concentration of the drug has overwhelmed the metabolizing enzyme or secretory pump. This is often referred to as *non-linear* or *Michaelis-Menten* elimination:

$$CL = \frac{V_{max}}{K_m + C_p}$$

• where $V_{max}$ is the concentration at which the rate of metabolism is half of the maximum rate, and $C_p$ is the drug concentration.

• Example: Phenytoin
Developmental Changes
Factors that change with development

- Gastrointestinal tract
  - **Gastric acid**: Neonates and infants typically have a gastric pH between 6 and 8. They typically absorb acid labile drugs such as penicillin G, amoxicillin, and erythromycin more efficiently than adults and older children, and absorb weak acids such as phenobarbital and phenytoin more poorly.
  - **Gut motility**: Gut motility significantly affects drug absorption. Whereas gastric emptying in adults is biphasic, with a rapid first phase (10-20 minutes) and a slower second phase, the process typically takes 6-8 hours in neonates and infants.
Factors that change with development

• Influence of food:
  – The influence of food on *gastric emptying* further complicates a drug’s pharmacokinetic predictability. The consumption of a fatty meal and subsequent entrance of lipids into the stomach inhibits gastric emptying and may affect passage of the drug into the small intestine.
  – **Intestinal transit time** is a factor that limits drug absorption. Marked variability in the intestinal transit time of neonates and infants, whose total gut transit time (for both the small and large intestine) may range between 8-96 hours versus 2-48 hours for an adult.
What is ontogeny of drug disposition?

• Ontogeny: the origin and development of an organism from the fertilized egg to its mature form (also *Ontogenesis* or *Morphogenesis*)

• Multiple organs that affect drug disposition undergo developmental changes:
  – gastrointestinal function
  – integumentary development
  – extracellular water (affects volume of distribution)
  – body fat (important for drugs with distribution in fat)
  – developmental changes in renal function
  – capacity of key metabolic enzymes
Specifcics of drug metabolism in the growing body

Metabolic capacity

Water distribution

GI function

Skin thickness etc.

Renal function

A

Changes in Metabolic Capacity

Percentage of Adult Activity

- CYP3A4
- CYP1A2
- CYP2D6
- UGT2B7

Age

- <24 hr
- 1–7 days
- 8–28 days
- 1–3 mo
- 3–12 mo
- 1–10 yr


Drug Dosing
Postnatal Adaptation of GFR

Filler G
Kidney Int.
2011;
80(6):567-8
Examples of ontogeny
Developmental changes of MPA exposure in children

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Abstract

Background Developmental changes (ontogeny) of drug disposition of Mycophenolate mofetil (MMF) have been understudied.

Methods The charts of 37 pediatric renal transplant recipients (median age 7.3 years, median follow-up 7.8 (IQR 6.6, 14.3 years) who had regular mycophenolic acid (MPA) trough level monitoring in combination with tacrolimus (n = 31) or sirolimus (n = 6) therapy were analyzed retrospectively for their dose-normalized MPA exposure, steroid dose, albumin, hematocrit, and cystatin C estimated glomerular filtration rate (eGFR). Using appropriate univariate and multivariate methods, we determined whether MPA exposure was age dependent when controlling for the confounders.

Results Dose-normalized MPA trough levels could be calculated in 2,128 (median 45/patient) instances. Spearman rank correlation analysis revealed that age correlated with dose-normalized MPA trough level for both body weight and body surface area, as well as serum albumin, hematocrit, steroid dose, and eGFR. In the multivariate analysis, serum albumin and steroid dose were not significant, and hematocrit only being significant when the youngest group of patients <6 years of age was compared. eGFR was the most important confounder, but age dependency remained significant when controlling for all confounders.

Conclusions Small children are at a significantly greater risk for low MPA trough levels than adolescents, highlighting the need for pharmacokinetic monitoring of MPA.

Keywords Kidney transplantation · Pediatric · Mycophenolate mofetil · Therapeutic drug monitoring · Mycophenolic acid trough levels · Ontogeny

Introduction
Characterization of sirolimus metabolites in pediatric solid organ transplant recipients


Abstract: Potential age-dependent changes of sirolimus metabolite patterns in pediatric renal transplant recipients remain elusive. Thirteen pediatric solid organ transplant recipients (10 kidney, one combined liver–kidney, two liver, mean age 8.0 ± 5.0 yr) underwent a sirolimus pharmacokinetic profile in steady-state with 10 samples drawn over 12 h post-intake to calculate the AUC_{0–12 h}. Concentrations of sirolimus and metabolite were quantified using a validated LC-MS/MS assay and metabolite structures were identified directly in blood extracts using LC-MS/iontrap. Average sirolimus AUC_{0–12 h} was 64.9 ± 29.7 ng h/mL. Median (range) AUC_{0–12 h} for each metabolite (ng h/mL) was: 12-hydroxy-sirolimus 7.6 (0.2–18.8), 46-hydroxy sirolimus 3.1 (0.0–12.4), 24-hydroxy sirolimus 4.3 (0.0–12.6), piperidine-hydroxy sirolimus 3.5 (0.0–8.3), 39-O-desmethyl sirolimus 3.6 (0.0–11.3), 16-O-desmethyl sirolimus 5.0 (0.1–9.9), and di-hydroxy sirolimus 4.3 (0.0–32.5). The metabolites reached a median total AUC_{0–12 h} of 60% of that of sirolimus. The range was 2.6–136%, indicating significant variability. In all, 77.5% of the metabolites were hydroxylated, while 39-O-desmethyl sirolimus accounted for only 8.4% of the AUC_{0–12 h}. This is clinically relevant as 39-O-desmethyl sirolimus shows 86–127% cross-reactivity with the antibody of the widely used Abbott sirolimus immunoassay. The metabolism of sirolimus in the children included in our study differed from that reported in adults, which should be considered when monitoring sirolimus exposure immunologically.

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Key words: sirolimus – blood metabolite patterns – age-dependent – pharmacokinetics – children

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Summary

• 61% of drugs are renally excreted and need to be adjusted for nephron endowment.

• Most of these drugs are excreted by tubular secretion, not by glomerular filtration.

• There are substantial developmental changes of kidney function in the first year of life that affect drug clearance.

• Knowledge of the pharmacokinetics, volume of distribution and plasma protein binding allow you to predict clearance by RRT.