PRINCIPLES OF PEDIATRIC PHARMACOTHERAPY

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References

[*] Pediatric Lexicomp
[*] Harriett Lane
Respiratory Rate

- Newborn: 30-60
- Infant (1-6 mos): 30-40
- Infant (6-12 mos): 24-30
- 1-4 years: 20-30
- 4-6 years: 20-25
- 6-12 years: 16-20
- Over 12 years: 12-16
Heart Rate

- Infant (0-1 yr) 120-160
- Toddler (1-3 yr) 90-140
- Preschool (3-6 yr) 80-110
- School Age (6-12 yr) 75-100
- Adolescent (12+yr) 60-90
## Blood Pressure

<table>
<thead>
<tr>
<th>Age</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>50-90</td>
<td>30-60</td>
</tr>
<tr>
<td>Infant</td>
<td>74-100</td>
<td>50-70</td>
</tr>
<tr>
<td>Toddler</td>
<td>80-110</td>
<td>50-80</td>
</tr>
<tr>
<td>Preschooler</td>
<td>80-110</td>
<td>50-78</td>
</tr>
<tr>
<td>Schoolage</td>
<td>84-120</td>
<td>54-80</td>
</tr>
<tr>
<td>Adolescent</td>
<td>94-140</td>
<td>62-88</td>
</tr>
</tbody>
</table>
Dosing Considerations

- Mg/kg/dose: most common approach
- Body surface area - used for select medications
- Suspension concentration or tablet/capsule size
- Age of patient
Dosing Considerations (continued)

- Renal function: reduced in neonates, good clearance in most children and adolescents (better than adults).
- Metabolism: Dependent on which enzymes used but may exceed adults throughout childhood. Adult values as adolescent.
- Volume of distribution depends on drug water or lipid solubility. In infancy and early childhood, water soluble drugs with larger volume of distribution.
- Drug doses: mg/kg up to adult dosing.
Aminoglycosides

Volume of distribution:
- preemie: 0.5-1.2 L/kg
- neonates: 0.5 L/kg
- infants: 0.4 L/kg
- children: 0.35 L/kg
- adolescents: 0.3 L/kg
- adults: 0.2-0.25 L/kg
Phenytoin

🌟 Volume of Distribution:

preemie: 1-1.2 L/kg
neonate: 0.8-0.9 L/kg
infants: 0.7-0.8 L/kg
children: 0.7 L/kg
adults: 0.6-0.7 L/kg
Calculation of CrCl in Children

- Traub and Johnson: CrCl = 0.48(ht in cm) divided by SCr
- Schwartz: CrCl = k(ht in cm) divided by SCr; k = constant that varies between age and gender of children
Drug Dosage Formulations: Oral

- Extemporaneous formulations: Solutions/suspensions
- May use solid oral, injectable formulations, or bulk powders to make.
- Flavoring agents
- Stability information
Drug Dosage Formulations: Intravenous

- Fluid restriction
- Limited IV access
- Lacking information on diluent amount
- Fluid volumes based on patient weight
- Infusion devices-offer lower rates
Children may react differently

- Children are similar to the elderly in some ways.
- Children may be more sensitive to drugs with extrapyramidal effects - such as prochlorperazine
- Antihistamines - may sedate or stimulate kids.
- Sedatives/pain medications
Practical Kinetics-Vancomycin Dosing

- Neonates
- Infants/Children
- Adolescents
- Select disease states:
  - Oncology
  - Meningitis
A 7kg infant is started on vancomycin 15mg/kg (100mg) IV q8h to treat an empyema. The trough prior to the second dose is 4. You are called for a recommendation on what to do. What do you recommend?
Vancomycin

An 8 year old 20 kg septic girl is treated with 300mg IV q8hr vancomycin. A trough is drawn prior to the 5th dose and it is 25. Her SCr is 1 and her urine output is 0.5ml/kg/hr but was 2 ml/kg/hr 8 hours ago. You are called what to do with the vancomycin dosing. What do you recommend?
Practical Kinetics - Gentamicin/tobramycin

🌟 Neonates
🌟 Infants/Children
🌟 Adolescents
🌟 Once daily dosing
**Gentamicin cases**

🌟 A 10kg infant is given 25mg IV q8hr gentamicin for a rule out sepsis. When should a peak and trough be drawn? A peak and trough are drawn and come back 10 and 2 respectively. What do you recommend? What questions do you ask prior to recommending?
Gentamicin cases

A 12.5kg 4 year old is being treated with gentamicin for enterococcal urosepsis. Levels are drawn around the 4th dose and come back 7 and 1.7. She will be treated for 1 more week. What do you recommend if any for dosage changes? What kind of follow up levels do you recommend?
**Level information**

- When to draw levels
- High trough
- Low trough
- High peak and trough
- High peak and low trough
Questions
Pediatrics and Medications

- Example medications: Chloramphenicol and tetracycline
- FDA Data: Only 33% of new medical entities with potential usefulness in pediatric patients and approved for marketing in 1997 had any pediatric indication.
- 80% of drugs used in children DO NOT have approved labeling.
Food and Drug Administration Modernization Act (FDAMA)

- Provides an incentive for drug manufacturers to develop specific information about pediatric uses and doses.
- A company may be able to extend its’ market exclusivity by 6 months by performing pediatric studies.
- Expires in 2007 (The extension is called the Best Pharmaceuticals for Children Act)
**Studies Breakdown Report For Issued Written Requests as of June 30, 2006**

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy &amp; Safety</td>
<td>254</td>
<td>35</td>
</tr>
<tr>
<td>PK &amp; Safety</td>
<td>208</td>
<td>29</td>
</tr>
<tr>
<td>PK/PD</td>
<td>62</td>
<td>9</td>
</tr>
<tr>
<td>Safety</td>
<td>111</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>98</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>732</td>
<td></td>
</tr>
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</table>
The FDA 1998 Pediatric Rule

- Mandates pediatric studies of medications.
- Older drugs requesting supplemental new drug applications for a new indication or use or new drugs may be required to obtain the pediatric information.
- Applies when the drug will be used for the same indication in children as adults and there is likely to be a “meaningful therapeutic benefit to children and absence of labeling poses a risk or there is substantial use …”)
Pediatric Rule Overturned

★ In October of 2002 the pediatric rule was struck down by the courts.
★ July 24, 2003-Senate unanimously passed legislation to endorse the Pediatric Rule.
★ December 3, 2003 President signed the legislation allowing the FDA to require pediatric studies.
The Pediatric Research Equity Act

- Expires in 2007
- Covers all new drugs and biologics
- Pediatric testing may be deferred if waiting for these studies would delay the availability of the adult product.
- May be deferred if studies in adults and older children need to be completed before testing in younger children or infants can be safely done.
The Results

- As of December 2002 a total of 264 drugs have received waivers.
- 129 of the above drugs have completed studies.
International Conference on Harmonization

- An effort to harmonize drug development among the US, European Union, and Japan.
- Pediatric drug development was reviewed and an official ICH document/draft was available in 2000.
Ethical Considerations

- Major issues related to inclusion of children in research studies involve:
  1. Consent/assent
  2. Assessment of risks and benefits
  3. Compensation and reward for participation
  4. Use of placebo
  5. Involvement of healthy children as research subjects.
Factors Placing Pediatric Patients at Increased Risk for Adverse Drug Reactions

★ Different and changing PK parameters between pts of various ages and stages.
★ Need for calculation of individualized doses based on the patient’s age, weight, BSA, and clinical condition.
★ Lack of available dosage forms and concentrations.
★ Need for precise dose measurement and appropriate drug delivery systems.
★ Lack of published info or FDA-approved labeling.
Medication Errors

- Mathematical errors
- Transcription errors
- Trailing zeros
- Not rounding to the nearest whole number
- Incorrect preparation- either compounding or drawing up wrong
Preventing Medication Errors

- Health care provider education is needed.
- The use of improved technology.
- Implementation of policies to enforce appropriate prescribing and preparation.
- Support of quality improvement program to oversee drug administration.
Compliance Issues

- Preparing correct dosage in an acceptable dosage formulation is only part of the process to ensure patient response.
- For non-hospitalized pts we need to increase emphasis on compliance.
- Studies show 30-70% compliance rates in kids
- Some of the poorest compliance is with asthma and epilepsy.
Compliance Issues (cont.)

- Forgetting to take doses and stopping after some improvement but before completing full course of therapy are 2 of the most frequent problems (same as adults)
- Inability to obtain drug due to lack of financial resources and the use of dosing schedule not compatible with the family’s routine occur and may be preventable.
Compliance

- Some feel palatability is the most important factor in compliance.
- A motivated, supportive parent can actually be the single most important factor in determining compliance.
Issues in Pediatric Compliance: Infants and Young Children

- Taste and palatability
- Dosing frequency
- School/daycare policies
- Adverse Effects
How to improve taste/palatability

- Oral liquid- sometimes chilling helps
- Sprinkle formulations if available
- Mix with food
- Tablet placed in gel cap if pt can swallow caps
- Chocolate milk/syrup or juice for bitter
- Commercially available medication flavorings
Issues in Pediatric Compliance: Older Children

- Autonomy
- Self-medication
- Adverse effects
- Peer-support
Compliance: Older Children (cont)

- OTC drug use increases in adolescents and prescription medication compliance decreases.
- Need to discuss:
  - Drug interactions fully with them
  - May need contracts or therapy diaries
Summary

- Dosing Considerations
- New Rulings
- Ethical Issues
- Medication Errors
- Compliance