Cough and Cold Remedies in Children: Pharmacokinetics

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Pharmacokinetics

- What the body does to the drug:
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Pharmacodynamics is what the drug does to the body

Absorption

- Can be affected by:
  - Gastric pH
  - Gut motility (transit time)
  - Food
  - Formulation: liquid formulations in general are more rapidly absorbed than tablets

Distribution

- Protein binding:
  - Neonates have different (decreased) concentrations of plasma proteins relative to older children and adults, but after the neonatal period there are few changes related to age

Metabolism

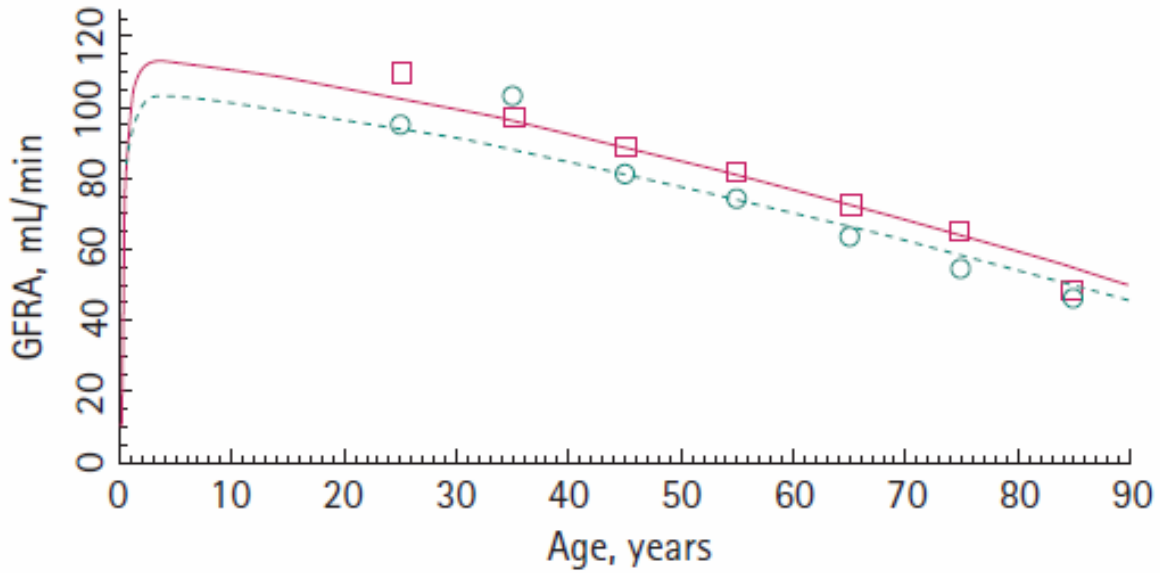
- From birth to 2 years of age there are major changes in the expression of drug metabolising enzymes:
  - CYP1A2 has negligible expression in the fetus, is detectable by 1 to 3 months age, and reaches adult levels by 1 year of age
  - CYP2A6 is not expressed in fetal liver and is developed by 1 year of age
  - CYP 2B6 appears to mature later than CYP2A6
  - CYP2C9 has no activity in fetal liver, but is detected by 1 day of age and activity matures to 50 % of adult activity by 1 month of age
  - CYP2C8 and CYP2C18 appear to parallel CYP2C9
  - CYP2D6 activity is present from 23 weeks gestation (25 weeks post-conceptional age), is not fully expressed at birth and reaches levels comparable to the adult activity by 1 year of age
  - CYP3A expression changes through development through changes in the relative and absolute expression of CYP3A4, CYP3A5 and CYP3A7. CYP3A7 expression is greatest in fetal liver and it is highly expressed through to 6 months postnatal age, but soon after birth its expression decreases and adult levels of expression are around 10% that of fetal. CYP3A4 expression is low in the fetal liver, but reaches 30-40% of adult expression by one month of age. CYP3A5 expression has high variability that appears to be independent of age.

Metabolism

- Dextromethorphan: CYP2D6
- Chlorpheniramine: CYP2D6
- Phenylephrine: MAO
- Brompheniramine: limited data, CYPp450

Maturation of Renal Function

FIG. 2. GFR/A from creatinine clearance data of Kampmann et al. [5]. Each point represents the mean GFR/A over a 10-year period. The solid line and red squares is the curve for males ($\beta_{sex} = 1.046$) and the dashed line and green circles, females ($\beta_{sex} = 0.954$). In the absence of mean ages for the range, the midpoint of each decade is assumed. The patient diagnosis was hypertension for 114 and chronic neuropathy for 106.



GFR/A = GFR per 1.73 m^2 of BSA

Wahl EF, Lahdes-Vasama TT, Churchill BM. Estimation of glomerular filtration rate and bladder capacity: the effect of maturation, ageing, gender and size. BJU Int 2003;91(3):255-62

Renal clearance

- Hence, there is a relative decrease in the renal clearance of drugs in infants:
  - Pseudoephedrine

Changes in PK from 2 years age

- Relate primarily to size, few developmental changes after 2 years:
  - Scale on basis of size: e.g. weight, weight$^{0.75}$

Calculations of Dosing

- Dosing for children traditionally has been calculated on the basis of:
  - Weight
  - Age
  - Weight and age (e.g. neonates)
  - Surface area
- Other novel methods:
  - Allometric scaling
  - Physiologically based modelling

Cough and cold mixture dosing

- Some cough and cold preparations have dosing recommendations based on age categories, but children's weights can be highly variable within an age category: e.g. 15 kg is around the 97th centile at 2 years and the 3rd centile at 6 years for boys

Hence

- Advances in understanding of drug disposition in children are not reflected in the dosing recommendations for cough and cold preparations