Pharmacology in pediatrics

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PEDIATRIC PHARMACOLOGY

- Drug use in children is mostly empiric
- Essential characteristic of childhood: growth and development

Basic thesis

„CHILD IS NOT A LITTLE ADULT!„

PEDIATRIC PHARMACOLOGY

- Main pharmacology principles similar in children and adults
  HOWEVER
- **Childhood is not homogenous** (ranges of body weight 1-70 kg!!)
  physiologic and morfologic distinctions in different stages of child development
  High variability in Pharmacodynamic (PD) response and Pharmacocinetics (PK)
  quantitative
  qualitative
- Most of differences: in perinatal period and in the 1st month of life

AGE GROUPS IN PEDIATRIC POPULATION

(European Medicines Agency EMA, ICH)

GROUP:	AGE:
immature newborn	gestational age < 38 weeks
preterm born	24 – 37 weeks
premature	38 - 42 weeks
Newborn	birth → 4 weeks
Perinatal period	39 week – 1week after birth
Infant	1 → 24 month
Child	2 → 11 years
Adolescent	12 → 17 years
Adult	≥ 18 years

SPECIFICS IN PEDIATRIC PHARMACOLOGY

- ***Dosage***
- ***Pharmacokinetics (PK)***
- ***Pharmacodynamics (PD)***
- ***Route of administration, drug formulations***
- ***Toxicity***

Dosage in pediatric patients

- No reliable method/ formula based on the adult dose which would guarantee efficacy and safety dose in child
- Dosage for children population is usually not stated by the marketing authorisation holder
- Calculation of the dose based on
  - Body surface area
  - Body weight
  - Age
- Keep in mind children specifics

Dosage in pediatric patient

⇒ **Body surface area (BSA)** – MOST APPROPRIATE PARAMETER FOR DOSE CALCULATION IN CHILDREN

particularly early months - years, at least up to 3 yrs of age

Relationship between kg and m^2 : example of 8 months infant	
weight 9 kg	cca 1/8 of the adult value
BSA 0.4 m^2	cca 1/4 of the adult value

⇒ *Dose for children should be equivalent to ¼ NOT to 1/8 of the adult dose*

Calculation (Approximation) of Pediatric Dose Based on Adult Dose

Clark's Body Area Rule - Formula based on BSA of the Pediatric Patient

$$\text{Dose for children} = \frac{\text{child BSA } (m^2) \times \text{adult dose}}{1{,}73\ (m^2)}$$

Body Surface Area

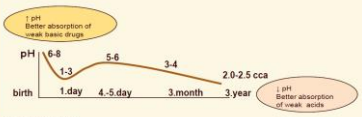
a) nomogram
b) Calculation

BSA – Body surface area

ABSORPTION - p.os. administration

1. Lower gastric acidity (↑ pH)

Gastric pH after birth is significantly changed



Consequences:

↑ pH ⇒ increased disociation of acidic drugs ⇒ reduced absorption from GIT, lower bioavailability (fenobarbital)

⇒ Decreased disociation of basic drugs ⇒ facilitated absorption from GIT, higher bioavailability (alkaloids, opioids, amoxicilin)

ABSORPTION - p.o. administration

2. Increased permeability of gastrointestinal mucosa: **(drugs, toxins, endotoxins, immunokomplexes) due to morphological specifics**
   - Wider intercelullar spaces
   - Finer epithelium structure
   - Immature barrier function of GIT membranes
3. Gastric emptying
   - Slower rate of gastric emptying - newborns
   - since 5.-6. month – GIT transit accelerated
   - Breastfeeding accelerates bowel movements
   - Impact of pathologic conditions (RDS, CHD)

RDS - respiratory distress syndrom
CHD – Congeital heart disease

ABSORPTION - p.o. Administration – cont.

4. Irregular and unpredictable peristaltic activity
5. Underdevelopped intestinal villi
6. Low activity of digestive enzymes
   lipase, amylase (alfa-amylase), protease
7. Low production of bile acid
   low absorption of lipofilic drugs minimally up to 4. month
8. Immature enzymes of active transport of drugs through membranes; cca in 6-8 monhts of age close to adult dose

In 1. month of life - rate and extension of GIT absorption are difficult to predict.

Therefore the oral drug administration is problematic at newborn age.

The parenteral application is preferred.

ABSORPTION p.o. in older children:

Oral administration - most appropriate route:

- anatomical a physiological conditions similar as in adults
- Absorption becomes more predictable
- **Faster transport through GIT**
  ⇒ shorter $t_{1/2}$ than in adults,
  - *Recommendation : Devide the daily dose to **4 partial doses** instead of 3 doses applicable for adults*

TRANSDERMAL ABSORPTION (local)

- Generally increased and variable in newborns/ infants
- incomplete stratum corneum
- Increased exposition of the drug/kg compared to the adult

Reason: higher BSA / body weight ratio, higher skin hydration

Toxicity as a result to transdermal absorption

Local **Glucokorticoids** – systemic effects
Boric acid – diarhoea, vomiting, convulsions
Aminoglycosid/polymyxin spray for burns - deafness

BSA = Body surface area

ABSORPTION - after I.M. administration

I.M. injection – **use only in exceptional cases**

- **Caution especially in dystropic, immobile children**
  - low muscle mass
  - low blood perfusion of the muscles
  - elimination of the muscle (and subcutaneous) reservoir is insufficient
  - Should the i.m. application be inevitable in newborns and small infants, then rather into the thigh muscle – more developped than m.gluteus
- Application of **strong irritant substances** should be avoided at all if possible/ or together with a local anestetic
- **Painfulness:** depot penicilin, streptomycin, erytromycin, hydrocortison
- **Complication i.m. applicaton infants:**

syndromes Hoigné (arteficial application of prokain PNC i.v.
syndrome Nicolau – arteficial i.a.application

ABSORPTION after rectal administration

- In newborns

Variable absorption
Low GIT motility
Frequent bowel movements
Advisable in anticonvulsive treatment

DISTRIBUTION
I. DISTINCTION IN BODY TISSUE COMPOSITION

- **The most significant pharmacokinetic difference between children and adults !!!**
- **proportion water : fat : dry mass** highly varies during developpment of the children's body
- **Water is the main distribution space** for most of drugs (EC)
- **Water balance in infants is extremely unstable** – mainly concerns EC water
  - impacts: temperature and humidity of external environment, feverish conditions, diet factors and fluid intake

Higher water proportion → impact on the DISTRIBUTON VOLUME V_D

- **total body water**:

pre-term newborn (1.5 kg)	80-85 %
full-term newborn(3.5 kg)	75 %
5-months infant (7 kg)	60 %
adult	55 - 60 %

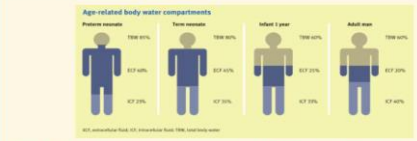
- **Extracelular water**:

immature newborn (1.5 kg)	60 %
full-term newborn (3.5 kg)	56 %
adult	30- 40 %

most drugs are distributed in EC space
hydrophilic drugs: increased Vd (fentanyl, thiopental)

Different composition of the children's body

HIGHER WATER PROPORTION → HIGHER V_D OF HYDROPHILIC DRUGS



LOWER FAT PROPORTION → LOWER V_D OF LIPOPHILIC DRUGS

DISTRIBUTION
II. DRUG - PLASMA PROTEIN BINDING

NEWBORNS

1. **lower afinity of plasma binding proteins to drugs**
2. **Reduced concentration of circulating plasma proteins**

Albumin - bound of acidic drugs (thiopental, phenytoin, diazepam), fatty acids, bilirubin

g1 – acid glycoprotein - bound of basic drugs (lidocain, alfentanil)

⇒ **increased free-drug concentration** *(fenytoin)*
⇒ **increased effect** (therapeutic and toxic)
⇒ **competition for protein binding**
drug– drug; drug - endogenous substances

bilirubin – risk of release from a protein bound to plasma
⇒ kernicterus (basal ganglia and brainstem)

drugs: Sulfisoxazol, fenytoin (free fraction in 1st month 11 %, adults. 3,6 % salicylates, theophylin, kofein, diazepam, thiopental, vit.K analogs

ADULT CAPACITY is REACHED CCA IN 1 YEAR

DISTRIBUTION
III. Permeability of blood-brain barrier

- immature BB barrier → higher permeability*(morfin)*
- more expressed in some patological conditions *(hypoxia, hypotermia, acidosis, meningitis)*
- **Faster onset and increased intensity of** therapeutically desirable but also undesirable/ toxic effects on CNS (herbal toxins, addictive substances, nicotin etc.)

DISTINCTION OF METABOLISM

- Immaturity of enzymatic systems **decreases liver elimination (lipophilic drugs)**
  - Phase I.reactions : oxidation, reduction, hydrolysis (CYP450)
  - Phase II.reactions: conjugations – glukuronidation, acetylation, sulfation, conj. with glutation
- Liver blood perfusion
- Mass of liver tissue – **impact on liver elimination**

METABOLISM
PHASE I. ENZYMES– OXIDATIVE METABOLISM

Development and maturation of CYP450:

- **prenatal:** most enzymes are functional in 30 weeks since gestation however activity is insufficient (fetus as a „slow metabolisator ") **= insufficient detoxication of substance from mother's blood**
- **postnatal:**
  variable maturation of individual isoforms
  fast maturation in first 4 weeks

Family P450: CYP1, CYP2, CYP3

METABOLISM
PHASE II. ENZYMES – CONJUGATION REACTIONS

- **Glucuronidation:**
  - **UGT capacity in peri- and postnatal period is very low**
  - **UGT activity reaches of adult values around 4th year of age**

Consequences of low UGT activity

- **Risk of accummulation of unmetabolised drug**
  ⟹ **potential higher toxicity**

Cisaprid - (prokinetic drug, H4 receptor agonist: cardiotoxicity with prolongation QT)

Chloramphenicol - ***„gray baby syndrome"*** described in 1959

UGT (UDP) = Uridin glukuronyltransferase, UDP-GT= uridin disfosfoglukuronyltransferase

METABOLISM
PHASE II. ENZYMES – CONJUGATION REACTIONS

Another types of conjugation reactions:

- **Sulfation** active already in 1st month, in some drugs *(paracetamol, acetaminofen)* replaces insufficient activity of other conjugation enzymes
- **Acetylation** (INH, sulfonamides) present at birth, but low activity, as in u SM

SM – slow metaboliser,

BIOTRANSFORMATION IN OLDER CHILDREN

Children above 2 yrs of age :

- **Faster drug metabolism**
- **Higher enzyme acitivity than in adults***

Examples

- teophylin ($t_{1/2}$ = 3.7 hrs. in school children, 5,5 hrs in adults)
- antiepileptics

Reason = higher liver mass related to the total body
i.e. higher number of functional hepatocytes

** Recommended using of smaller doses in more frequent intervals*

RENAL EXCRETION

- Glomerular filtration – passive diffusion
- Tubular secretion - active process, energy dependent channels or pumps
- Most drugs or their metabolites are excreted by kidneys

RENAL EXCRETION
I.Glomerular filtration (GFR)

- Glomerules are **morphologically** developped in week 36 after gestation
  BUT a) **functionally** totally unmatured in postnatal period
  b) very low kidney blood perfusion
  ⇒ *GF in neonate = cca 10 ml/min*
- GF accelerates extensively during first days after birth, 90% of the adult value is achieved around ½ year of age at the latest
- *Complete maturation up to 12 months*
- *Risk of drugs/ active metabolites accumulation* in those that undergo renal elimination *(aminoglycosides, cephalosporin)*

RENAL EXCRETION
II.TUBULAR SECRETION: (TS)

- Minimal after birth
- Tubules functionally immature
- Maturation in 12-18 months
- Adult value achieved in 24 months
- Up to 24 months – risk of drug accumulation, $T_{1/2}$ prolongation

PHARMAKODYNAMIC SPECIFICS:

- **I. Quantitative**
- **II. Qualitative**
  - A. Paradoxical drug response
  - B. Specific adverse events
  - C. Specific indication in pediatrics

I. QUANTITATIVE DIFFERENCE in CHILDREN RESPONSE

- **DIGOXIN** –seemingly better tolerance of higher doses
  ↓ both intrinsic activity and binding capacity of receptors
  - *Important role of PK factors -*
    distribution volume, binding plasma proteins capacity, elimination etc.

  Summary of both PD and PK = prolongated T1/2
- **SUXAMETONIUM** (peripheral myorelaxans) ↓ reactivity
- **THEOFYLIN, KOFEIN** ↑ reactivity
- Some antiepileptics
  SODIUM VALPROATE – ↑risk of hepatotoxicity
  LITHIUM – ↑ toxicity

II. QUALITATIVE DIFFERENCES
A. PARADOXICAL REACTIONS TO DRUGS

Converse effects on CNS

- Stimulation effect instead of inhibition:
  1.some hypnosedatives: ***fenobarbital***
  2. benzodiazepins: ***midazolam, klonazepam***
  3. H1-antihistaminics: ***promethazin***
  dimetinden (FENISTIL)
- Inhibitory effect instead of stimulating effects
  sympatomimetic „stimulating" amins: ***amfetamin***
  → *sedation*

II. QUALITATIVE DIFFERENCES
B. SPECIFIC ADVERSE EVENTS

Examples:

- **Tetracyclins** – deposits in teeth and bones - dysplasia of dental enamel growth impairment/ long bones
- **Glucocorticoids** – growth retardation, hormonal dysfunction
- **Fluorochinolons** – cartilage growth disturbance
- **Antipyretics/analgetics**: specific reactions
  - ✓ Aspirin – Ray syndrom
  - ✓ Pyrazolon analgetics – convulsion risk
  - ✓ Antiepileptics - frequent skin reactions
  - ✓ Opioids – breath depression

II. QALITATIVE DIFFERENCIES
C. SPECIFIC INDICATIONS IN PEDIATRICS

Indications that do not occur in adults and that are treated even in premature newborns:

- RDS „respiratory distress syndrome"
- Meconium Aspiration
- Apnoic pause
- Ductus Arteriosus Patens

Formulation, route of administration

- Oral
  - Liquid formulation preferred
    - faster absorption
    - Risk of less precise dose delivered (measuring cup, spoon)
    - Risk for drugs with tight relationship
      - C_{max} and toxicity
      - Low plama concentration and insufficient effect
- Solid formulations not recommended up to 3yrs
- neonates-often i.v. admin. – garantee of adequate concentration

Adverse events (AEs) in children – general principles

- Most AE accordant with those in adult population
- Limited experience and knowledge in new drugs
- Lack of clinical trials in pediatrics
- Common off-label use (up to 70% drugs)
- Most common: skin, gastrointestinal, systemic
- Most commonly used drugs: vaccines, antibiotics, antipyretics, non-steroid antiflogistics, drugs for cold, GIT
- Newborns more sensitive to AEs

Drug toxicity in newborns

- Sulfonamides
  - Competition with bilirubin in plasma protein binding sites
    - ↑ free bilirubin fraction
    - Low rate of bilirubin conjugation (immature enzyme UDP-GT)
    - Transfer of the free unconjugated bilirubin through HE barrier
    - Deposits in to basal ganglia and brain stem (kernicterus described 1956, relationship with bilirubin clarified 1964)
    - Toxicity (acute hyperbilirubinemic encefalopatia – first week after birth)

UDP = glukoronyltransferase

Drug toxicity in newborns cont.

- Chloramphenicol and „gray baby syndrom"
  - Insuficient glucuronidation reaction (1959)
  - Accumulation of toxic metabolites (vomiting, breathing distress, gray cyanosis, CV collapse)
  - Chloramphenicol in newborns contraindicated
  - If the dose was reduced from 100 to 50 mg/kg, syndrome di not occur
- Percutaneous toxicity
  - Methemoglobinaemia – anilin dye (1886)
    - Cyanosis in newborns, 17 deaths
  - Hexachlorophane – neurotoxicity

DRUG TOXICITY IN CHILDREN

- **Sodium valproate and hepatotoxicity up to 3 yrs**(1979)
  - described > 100 deaths
  - Abnormal drug metabolism up 3 yrs of age
    - Reduction of detoxication route (fatty acids oxidaton)
    - Increased activity of a specific cytochrom P450 – formation of hepatotoxic metabolites
- **Salicylates and Rey syndrome (1963)** - liver failure + and encefalopatia (reduced elimination of NH3)
  - viral infection
  - (1960, 1980)
  - Use restricted in viral infections up to 12 yrs
  - Later even restriction up to 12-16 yrs
- **Propofol a metabolic acidosis**(1990)
  - 12 deaths
  - Pacients who usually were on higher doses
  - Mechanism is not known

paracetamol and ibuprofen are the only antipyretics reommended in childrenn

FORMULATION ERRORS IN CHILDREN

- Diethylenglycol
  - Solvent for sulfonamides (1937, USA)
    - 76 deaths(children and adults)
  - Solvent for paracetamol
    - 47 deaths– Nigeria 1992
    - 51 deaths – Bangladesh 1995
    - 85 deaths - Haiti 1998
- Benzylalcohol – antibacterial properties, used in ampoules NaCl and water for intravenous administration (1982, USA)
  - 10 deaths of preterm neonates
- Emulsifier used in vitamin E injections (1984, USA)
  - 38 deaths of newborn
- Hexachlorophene in baby powder (1972, Francie)
  - Neurotoxin
  - 206 cases of encefalopatia, 36 deaths

Clinical trials in pediatric population

- **20% EU population (i.e. over 1 million in 25 countries) children < 16 years**
- **> 50 % drugs used in children and 90% drugs used in newborns were never evaluated for use in children**
- **drug use in children is more or less empiric (off-label)**
- **Risks:**
  - **Adverse event, potentially permanent**
  - **Overdosing**
  - **Inefficacy in underdosing etc.**

Practical issues related to clinical trials in pediatrics

- Introduction of a new drug into the pediatric practice is a higher-risk than in adult population
  - Clin. trials take longer
  - More complicated
  - More expensive (lower profitability)
  - Often ethical issues
  - Informed CONSENT from both parents
  - ASSENT from the child relevant to the age
  - Lack of experienced pediatricians – sites and investigators

CLINICAL TRIALS IN PEDIATRIC POPULATION– tailored approach

- PK studies – use of techniques adapted to specific population (salive collection instead of blood), minimalisation of patient burden
- PD studies – search for valid biomarkers (indicator of biologic process, patol. process or treatment response)
- Increasing research activity in infancy