Principles of Paediatric Clinical Pharmacy

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Brief introduction

- Serve as Senior Clinical Pharmacist in the HK University-Shenzhen Hospital, 福田区, 深圳.

- Opens in July, 12 for out-patient; Oct, 12 for in-patient.
- A& E Paeds Dept & Paeds ward service started in June, 13. PICU, Neonatal unit will also be opened soon.

Brief introduction

- Graduated from the University of Nottingham in the UK as BPharm Pharmacy.
- Completed pre-reg training in a hospital in the UK.
- Received the basic grade Hospital Pharmacy training in one of the London teaching hospitals.
- Completed the Diploma in Pharmacy Practice in London with completion of three clinical modules and one of them is paediatrics.

Paeds background

- St Mary's Hospital, Paddington, London – one year paeds training (general paeds, PICU, Paeds HIV, paeds bone marrow transplant, paeds meningitis, infectious diseases, satellite paeds pharmacy dispensary).

- King's College Hospital, London – 12 years training (PICU, general paeds, paeds liver, paeds oncology & haematology, paeds neurology, paeds surgery, paeds cystic fibrosis, neonatal medicines).

  Obs and Gynae – drugs use in breastfeeding/pregnancy.

- Published 2 paeds liver articles, wrote a chapter for a textbook, and involved in guidelines development & risk management.

Paeds background

- Nationally, I was involved in the DOH MCRN (Medicines for Children Research Network) Pharmacy and Pharmacology group. Work with research scientists and medical doctors to try to achieve the following aim.

  The aim of this group is to foster research and to improve the conduct of research which ultimately help to improve the health and well being of children.

- CPPE (Centre for Pharmacy Postgraduate Education) in England – funded by DOH. Acted advisory role.

Paeds Clinical Pharmacy Groups in UK

- Neonatal and Paediatric Pharmacy Group (NPPG)
- London Paediatric and Neonatal Group (LPPG)
- National PICU group
- National Paeds Oncology Group
- National neonatal ITU group
- National Liver Pharmacy Group (adults and paeds)

Advanced Clinical Pharmacy System in UK

- Specialised Pharmacists attach to the consultant – led ward round. Can change Rx on the drug charts and write discharge prescriptions.

- Supplementary Prescribing Pharmacist

  Pharmacist can prescribe drugs to patients according to an agreed Care Management Plan (CMP) e.g. in hepatitis clinic.

- Independent pharmacist prescriber

  This pharmacist can prescribe any drugs including unlicensed and most of the controlled drugs within his/her expert competency, such as paeds asthma clinic or post transplant clinic.

Advanced Clinical Pharmacy in the UK

- Consultant Pharmacist

- In the UK, a **consultant pharmacist** refers to a pharmacist who has advanced roles in patient care, research and education in a specific medical speciality or expert area of practice.

- E.g. PICU, Paediatrics, or Medication safety.

- The UK DOH creates this position intended to improve patient care by retaining clinical excellence within the NHS and strengthening professional leadership. He/she will form a dynamic link between clinical practice and service development to support new models for delivering patient care.

Lecture Plan

- **Objectives for the first session**

  To know and understand:

  → the definition of age.

  → a brief definition of paediatrics

  → differences between adult and children medicines.

  → unlicensed, ‘off-label and named patient products.

  → special manufacturer and extemporaneously preparations.

  → Pharmacokinetics in Paediatics.

  → Dosage calculations in Paediatics and Neonates.

  → Dose adjustment in renal failure in children

Lecture plan

- To know and understand:

  → Routes of administration in paediatrics

  → Different reference sources for paeds dosages.

  → Patient compliance in paeds.

  → Patient counselling in paeds

  To complete:

  → Paediatric dosage calculation exercises

Different periods of childhood

- **Term Neonates** – 0 – 27 days
- **Infants** – 28 days to 11 months
- **Children** – from 1 year to 11 years
- **Adolescent** – from 12 years to 16/18 years (depends on region)

>>>

- **Full term baby** – born between 37 - 42 weeks gestation
- **Premature baby**–born before 37 weeks gestation
- **Post conceptual age** – gestational age at birth + post-natal age.

What is Paediatrics?

- is the branch of medicine dealing with the **development, disease and disorders of children**.
- The various organs, body systems and enzymes that handle drugs develop at different rates.
- Paediatrics are separated from **adult medicines** by the **growth and development** throughout childhood.

What is Paediatrics?

- Children should not be treated as ‘small adults’ in terms of psychological,

  medical,

  pharmacological, and
  pharmacokinetics (ADME).

- Is Paediatrics a **speciality**?

  Paediatrics seems to be a specialised area, yet children experience the same range of illnesses that can affect adults such as asthma and cancer.

What is Paediatrics?

- Is Paediatrics a **speciality**? (to cont')

  Neonatology can probably be regarded as a speciality in its own right with different clinical situations and huge difference in pharmacokinetics and dynamics.

Unlicensed and ‘off label’ products

- ‘**Unlicensed**’ products: are defined as those products that have not been subjected to the licensing process.
- ‘**Off labels**’ products mean that they are being used outside the term of license.
- **Unlicensed and off-label products** are common in paediatrics as most of the drugs used in paediatrics are not extensively researched.
- **The safety, efficacy and quality** of these products cannot be guaranteed as they are not supported by the reassurances that the licensing system was introduced to provided.

Unlicensed and ‘off label’ products

- **Unlicensed and off-label products** does not imply inappropriate prescribing. It purely reflects the lack of available evidence to support the use in children.

- The responsibility of the unlicensed and off-label prescribing **will lie with the prescriber**.

- The decision to prescribe these products must be based **on the best interest for the child and there are no suitable alternatives.**

Unlicensed and ‘off label’ products

- Health professionals should have ready access to **sound information** on any medicine they prescribe, dispense or administer.
- As a pharmacist, you should obtain sufficient evidence to support the **unlicensed or off-label** prescribing before the supply of the medicine.
- In general, **it is not necessary to obtain the explicit consent** of parents, carers or child patients to prescribe or administer unlicensed medicines (as this is not clinical trial drug).

Unlicensed and ‘off label’ products

- **Examples of unlicensed or off-label products**
  - * Product imported from another country:
    Vit D injection imported from an European country
  - * IV Gentamicin was used orally for the indication gut decontamination.
  - * Oral Alendronic acid was used under 12 years old for the treatment of low bone density (not licensed for this age group).

Unlicensed and 'off label' products

- **Examples of unlicensed or off-label products**
  - * Crush tabs and dissolve in water such as crushing Clobazam tabs for an epileptic patient.
  - * Aspirin is contraindicated in children under 16 years old but is used in children with Kawasaki disease.
  - * Rifampicin is used to relieve the itchness symptoms in liver patients (different indication).

Other products used in Paediatrics

- **Named patient products:**

  * When a drug company supplies an unlicensed medicinal product on a named patient and consultant basis.

  * Example: one of the hospitals in London supplied named patient medicinal products for patients under the care of the speciality of paediatric allergy.

Other products used in Paediatrics

- **Special manufacturer preparations**

  * They are made by manufacturing unit holding **a manufacturer's licence.**

  Example: Magnesium Glycerophosphate liquid

- **Extemporaneous preparations**

  * They are made **on an individual basis** in pharmacy and are **not subjected to full quality assurance.**

  Example: Sodium bicarbonate 8.4% oral solution

Paediatric Pharmacokinetics

Pharmacokinetics in Paediatrics

- **Pharmacokinetics** involves study of the rates of **absorption, distribution and elimination.**
- Many changes occur in the way infants and children which may affect the drug handling from birth to adulthood.
- It is important to know the changes of pharmacokinetics throughout different stages of childhood in order to understand how paediatric doses are derived.

Pharmacokinetics in Paediatrics

(1) Absorption

- Few clinically significant alternations in older infants and children compared to adults; relevant changes apply to neonates usually.
- **Different routes of absorption**

  * Oral
  * Intramuscular
  * Percutaneous (skin)
  * Rectal

Pharmacokinetics in Paediatrics

(1a) Oral Absorption

- **Factors that affect oral absorption**
  * gastric emptying time
  * changing pH of the stomach
  * disease states
  * biliary function

- **In term neonates**, the gastric pH varies between 6 and 8 at birth, dropping to 2 to 3 within the following few hours.

- **After 24 hours of birth**, the gastric pH rises again to pH 6 – 7, gradually **falling to adult values by 20 to 30 months.**

Pharmacokinetics in Paediatrics

- **In premature neonates,** the high gastric pH (6- 8) is prolonged.
- Because the **immature gastric mucosa leads to reduced acid secretion.**
- This **high gastric pH** environment will affect one of the physiochemical characteristics of the drugs such as **ionisation** which will then affect **the extent of oral absorption** when compared with older children and adult.

Pharmacokinetics in Paediatrics

- As drug molecules must be unionised (not broken down by gastric pH) to be absorbed, the extent or rate of absorption of **basic drug** (such as penicillin) may be expected to increased (cos of ↓ drug breakdown)
- However, for those of **acidic drugs** such as phenytoin and phenobarbital), the extend of absorption may be **decreased** during the pre-mature neonatal period.
- Different oral doses may be required to achieve therapeutic plasma concentrations (e.g. **larger doses** of phenobarbital on a weight [mg/kg] basis)

Pharmacokinetics in Paediatrics

- **Gastric emptying and intestinal motility** affect the rate at which drugs are absorbed.
- **Gastric emptying time** usually approaches adult values at **about 6 months of age**.
- In the **1st 6 months of the infant**, peristalsis is reduced and gastric emptying is relatively slow, therefore **the rate at which most drugs are absorbed may be expected to be slower and the time to achieve maximum plasma levels may also expected to be ↑.**

Pharmacokinetics in Paediatrics

- **Disease states** may have impact on oral drug absorption.
- **Vomiting or diarrhoea may reduce absorption and** may result in acutely reduced therapeutic efficacy in chronic disease such as epilepsy**.**
- **Another example: Tacrolimus**. The plasma level of the drug will be affected if the patient has diarrhoea.

Pharmacokinetics in Paediatrics

- **Gastro-oesophageal reflux disease (GORD) can affect absorption** and may require dose alteration as the disease is treated; oral absorption of drugs may be reduced, necessitating higher oral doses initially which may require subsequent dose ↓ once GORD is controlled.

Pharmacokinetics in Paediatrics

- **Biliary function** also affects oral absorption.
- **Biliary function** affects the ability to solubulise and absorb lipophilic drugs.
- Immature transportation and secretion of biliary salts in the neonatat period may affect drug absorption.

Pharmacokinetics in Paediatrics

(1b) Intramuscular absorption –

- The rate and extend of absorption of a drug given by IM route depend on blood flow to the muscle.
- In **neonates**, they have

  * reduced skeletal muscle mass

  * reduced muscle blood flow

  * insufficient muscle contractions
- All the above factors make IM drug absorption **slower and unpredictable in neonates, particularly if premature or paralysed.**

Pharmacokinetics in Paediatrics

- The reduced muscle mass in **premature neonates** may also predispose to muscle damage if too great a volume of drug is injected.
- esp. problems in neonates as the **muscle mass is small** and the **blood flow through the muscle tissue** may not reach the adult proportions → **affects the rate of drug absorption → may be unpredictable.**
- Practically, I.M. injection is painful and distressing.
- This route **should be avoided** if other alternative routes can be used.

Pharmacokinetics in Paediatrics

- **(1c) Percutaneous absorption** – it is inversely related to the thickness of the stratum corneum and directly related to skin hydration.

- Neonates have **thin stratum corneum and high level of hydration;** premature neonates have an **immature epidermal barrier** to skin absorption.
  → ↑ **percutaneous absorption of topical drugs**

- The stratum corneum layer is even **thinner** in **preterm neonates**, hence further ↑ percutaneous absorption.

Pharmacokinetics in Paediatrics

- The ratio of surface area to body weight in neonates, infants and young children **is far greater than** in adults, → ↑ **percutaneous drug absorption → may lead to toxicity of some of the topical drugs,** e.g. corticosteriods, povidone-iodine
- Use of **topical and potent cream** to large areas or onto broken or burnt skin can result in **significant systemic absorption**, e.g. corticosteriods.
- Liberal use of **corticosteriod** creams on the skin of newborn infants, especially pre-term, may lead to **Cushinoid** effects if continued for more than 1 week

Pharmacokinetics in Paediatrics

- **(1d) Rectal absorption**
- Rectal administration is appropriate when nausea, vomiting seizure activity preclude the use of oral route.
- Diazepam rectal solution is particularly useful when children have either febrile convulsions or recurrent, poorly conrolled epilepsy when immediate Iv access is not possible.
- The rectal solution of diazepam has a better rate and extent of absorption compared to the suppository formulation.

Pharmacokinetics in Paediatrics

- **(1d) Rectal absorption**
- The longer the period the rectal dosage form to be retained, the greater the amount to be absorbed.
- For this reason, the rectal liquid should be placed well up to rectal vault.
- In neonates, the rectal absorption of drugs may be slow and unpredictable, although it is a useful route while other methods are not available.

Pharmacokinetics in Paediatrics

- **(1d) Rectal absorption (cont')**

- The absorption of drugs from the rectum is affected by **the rate of expulsion**.

- **Infants have a greater number of rectal contractions** than adults, which may **enhance the expulsion of the dose and reduce absorption of drugs such as paracetamol.**

Pharmacokinetics in Paediatrics

(2) Distribution

- **Changes in body composition** that occur during development alter the way that drugs are distributed round the body, hence to affect the dosage recommended for different age groups.

- The most dramatic changes in body composition occur **in the first year of life** but changes continue throughout development through puberty and adolescence, particularly **the proportion of total body fat.**

Pharmacokinetics in Paediatrics

(2) Distribution

- The **total volumes of body water & extracellular fluid** are the **greatest during the neonatal period and infancy**.
- The total water content in the **new born** is about **75% (85% in preterm; 60% year 12; 55% adult)**
- This will result in **larger** apparent volume of distribution **(V of D)** of drugs that distribute into these spaces and lower plasma concentrations for the same weight-based dose.

Pharmacokinetics in Paediatrics

(2) Distribution (cont')

- **E.g. Water-soluble drugs (Aminoglycosides)** → have the largest V of D in the newborn and young infants.

- Larger dose of aminoglycosides on a mg/kg basis is needed for the neonates.

Pharmacokinetics in Paediatrics

(2) Distribution cont'

- **Blood brain barrier** – BBB may be **functionally incomplete in the neonates** → allows increased penetration of some drugs such as antimicrobial penetration into the CSF for the tx of meningitis.

Pharmacokinetics in Paediatrics

(2) Distribution cont'

- **Protein binding** can also affect drug distribution.
- In **neonates and early infancy**, serum albumin and total protein concentrations are lower than adult values, hence ↓ drugs binding to proteins in the blood in these age groups.
- The serum albumin and total protein concentrations will gradually **reach adult values over the first year of life.**

Pharmacokinetics in Paediatrics

(2) Distribution cont'

- In addition, in **neonates and early infancy,** there is a **reduced affinity for the protein binding sites** because there are other endogenous substances such as bilirubin and free fatty acids which are also competing for the same binding sites.

Pharmacokinetics in Paediatrics

(2) Distribution cont'

- Therefore, in **infancy,** the plasma level of phenytoin does not need to be as high as adult value as more of the phenytoin are unbound and thus active to be effective (and toxic).

- The normal range in **neonates is 6 to 15 mg/L**, compared to 10-20mg/L for children and adults.

Pharmacokinetics in Paediatrics

(3) Drug metabolism

- One of the factors that affect the drug plasma concentrations is the ability of the child to remove (eliminate, clear) the drug from the body.

- This will normally involve **metabolism (via the liver) and/or excretion of unchanged drug in the urine.**

Pharmacokinetics in Paediatrics

(3) Drug metabolism

- The primary organ for drug metabolism is **the liver.**

- **At birth,** the majority of hepatic microsomal enzymes are either **absent or present in small amounts**; particularly in **pre-term infants** → ↓ capacity of drug metabolism.

Pharmacokinetics in Paediatrics

(3) Drug metabolism

- This leads to **longer plasma half lives and increased plasma concentrations** in hepatically cleared drugs in premature babies and in new born. The more premature the neonates, the more depressed the hepatic metabolism.

Pharmacokinetics in Paediatrics

(3) Drug metabolism

- **Hepatic phase I reactions** (i.e. oxidation, reduction, hydrolysis) appear to mature over the first few months of life, and gradually reach adult metabolic capacities at **six months of age.**

- **Hepatic phase II reactions** (such as acetylation and glucuronidation) increases significantly over the first 2 to 3 months of life and fully mature by about **three months of age.**

Pharmacokinetics in Paediatrics

(3) Drug metabolism

- In age groups 1-9, **metabolic clearance of drugs is shown to be greater than adults.**
- **E.g. theophylline**. Children of age 1-9 has theophylline clearance higher than adults and young infants → need higher dosages (mg/kg).
- This is thought to be due to the fact that, relative to the body size, the liver is larger than adults.
- In adolescence, the drug metabolic rate reduces to adult value.

Pharmacokinetics in Paediatrics

- Another e.g. - use of **chloramphenicol** in infant for the tx of meningitis.
- The enzyme system responsible for **conjugation of chloramphenicol** starts to develop a few days before birth and fully matures towards the end of the first month.

Pharmacokinetics in Paediatrics

- Dosage – **Premature and full term infant -**

  25mg/kg/24hrs

  First week after birth:

  50mg/kg/24 hrs

  Over 4 weeks of age:50–100mg/kg/24hrs.

- **Toxicity can lead to Grey Baby Syndromes in infants.**

Pharmacokinetics in Paediatrics

(4) Excretion

- Renal excretion depends on **glomerular filtration rate (GFR),** and **tubular reabsorption/secretion**.

- GFR at birth is highly dependent on gestational age but increases rapidly over the first week of postnatal life and reaches adult values by **about three months of age.**

Pharmacokinetics in Paediatrics

(4) Excretion

- Tubular secretory and resorptive capacity appears to mature more slowly, approaching adult values at about **seven months of age.**

Pharmacokinetics in Paediatrics

(4) Excretion

- **Preterm infants** – GFR < 1/6 of a child or adult, leading to extended half-lives of renally cleared drugs such as aminoglycosides.

- **Dose intervals** of renally excreted drugs must take into account the development and variability of renal function in the neonatal period to avoid potential toxicity.

Pharmacokinetics in Paediatrics

4) Excretion (cont')

- The dose used in preterm neonates must be individualised to reflect maturational and treatment-associated changes in renal function.

- Aminoglycosides have been well studied. Dose intervals as long as 36 to 48 hours may be required in preterm neonates to avoid accumulation.

Drug calculations in paeds

Dosages Calculations in Paediatrics

- **Children are not mini-adults**; dosages should not be calculated from the proportion of the adult dose.

- Weight, height and age are more accurate parameters to calculate paediatric dosages.

- Most doses of drugs have been derived from trials or from clinical experience and are expressed as mg/kg basis.

Dosages Calculations in Paediatrics

- In general, paediatric dosages may be calculated using age, body-weight or body surface area, or a combination of these factors.

Dosages Calculations in Paediatrics

1) **Age ranges:**

Drugs with high therapeutic index, e.g. penicillin, single doses may be quoted for a wide age range.

Dose recommendation for Oral Penicillin V are:

1 month to 1 year: 62.5mg QDS

1 to 6 years: 125mg QDS

6 to 12 years: 250mg QDS

12 to 18 years: 500mg QDS

Dosages Calculations in Paediatrics

2) Body weight

- Body weight may be used to calculate doses expressed in **mg/kg**. Young children may require a higher dose per kg than adults because of their high metabolic rates.

- Other problems need to be considered. For example, calculation by body-weight in the overweight child may result in much higher doses being administered than necessary; in such cases, dose should be calculated from an ideal weight, related to height and age.

Dosages Calculations in Paediatrics

Body weight (cont')

- **The adult maximum dose** is always needed to take into account when using body weight for dosage calculation.

- Example: the recommended dose for IV Teicoplanin is 10mg/kg/dose for age group of 1 month to 18 years old. For a 50kg child, the prescribed dose should be 400mg OD as the maximum dose of IV Teicoplanin is 400mg OD.

Dosages Calculations in Paediatrics

- Another example of a drug using mg/kg basis.

  Cefalexin oral suspension.

  * Neonates 7 to 21 days: 25mg/kg TDS
  * Neonates 21 to 28 days: 25mg/kg QDS
  * Child 1 month to 12 years: 12.5mg/kg BD

Dosages Calculations in Paediatrics

3) Body surface area (BSA)

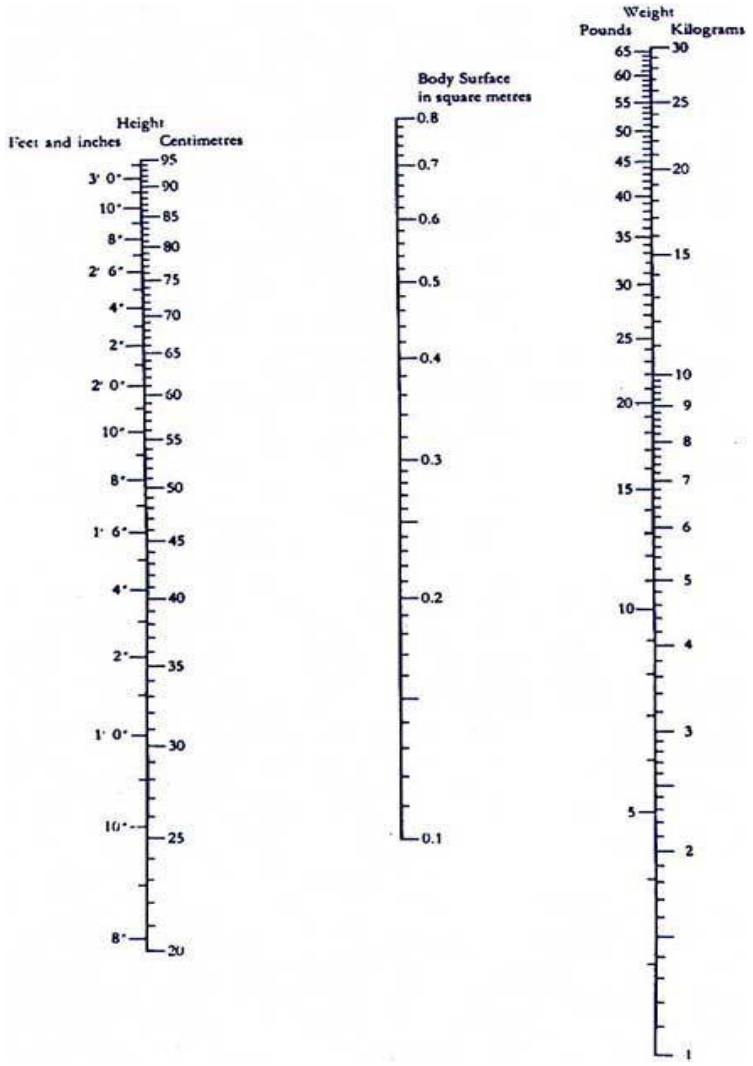
- The method of using BSA is most accurate and reliable method for calculation of paediatric doses as BSA reflects changes in:
  - *** cardiac output**
  - *** fluid requirements**
  - *** body composition**
  - *** renal function.**

Dosages Calculations in Paediatrics

- **BSA** can be calculated from a **nomogram or a formula.**

Dosages Calculations in Paediatrics

- **BSA** nomogram



Dosages Calculations in Paediatrics

- **BSA** can also be calculated from a **formula.**

- The formula is $\frac{[\text{weight (kg) x height (cm)}]}{3600}$,

  then **square root the whole thing**.

- However, determining BSA can be time-consuming and impractical.

Dosages Calculations in Paediatrics

- Accurate height and weight may be difficult to obtain in a sick child and manufacturers rarely provide dosages on BSA basis.

- Use BSA as method of dosage calculation is generally **reserved for potent drugs** where there are small differences between efficacious and toxic doses (**narrow therapeutic index**).

Example: a cytotoxic drug called IV Vincristine

Dosages Calculations in Paediatrics

- In general, in Paediatrics, the most widely used method of calculation is **in mg/kg basis.**

Dosage adjustments in renal failure in paeds

Dosages adjustment renal failure in Paediatrics

- The dosage adjustments for renal function should be made based on glomerular filtration rate (GFR), by **calculating the estimated creatinine clearance** (refer to the equation in the next slide).

- Use the equation, adapted from Morris et al (1982), for children aged <18 years. This equation may be used for infants although it is not a reliable method.

Dosages adjustment renal failure in Paediatrics

"Estimated" ClCR (ml/minute/1.73 m^2) = $\frac{X \times ht}{SCR}$

Where ClCR = Creatinine clearance in (ml/minute/1.73m^2)

SCR = Serum creatinine in micomol/litre

Ht = Height in cm

X = Correction factor

X = 25 for preterm babies

X = 35 for term babies

X = 40 for prepubertal children

X = 50 for adolescents

Drug prescribing in neonates

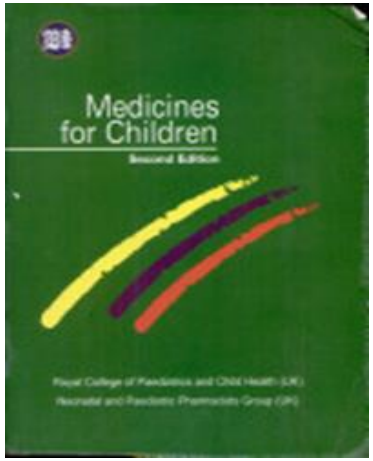
- Neonates differ greatly from adults in their responses to drugs.
- Special care is needed in the neonatal period (first 28 days of life) and doses should always be calculated with care; the risk of toxicity is increased by reduced rate of drug clearance and differing target organ sensitivity.
- Neonates is a speciality on its own right.

Reference sources and formularies used in paeds

Reference sources/drug formularies in paeds

a) Formularies

- British National Formulary for children 2012-2013
- Chinese National Formulary for children (Jan, 2013)
- Guy's and St Thomas's, King's College and University Lewisham Hospitals Paediatric Formulary (8th edition)
- Medicines for Children (2003), Royal College of Paeds and Child Health, UK



Reference sources/drug formularies in paeds

- Northern Neonatal Formulary, UK
- ‘Drug doses’ by Frank Shann, Intensive care unit, Royal Children’s Hospital, Melbourne, Australia (15th edition, 2010).

Reference sources/drug formularies in paeds

b) **Local Clinical Guidelines**

In hospitals with well-established clinical specialities, they have clinical guidelines such as drugs use in paeds liver diseases and drugs use in paeds cystic fibrosis.

c) National guidelines:

NICE guidance (e.g. meningitis, paeds sedation), DOH guidelines, Royal College of Paediatrics and Child Health

Paediatric forum – a focus on medications use

Paediatric forum – a focus on medications use

- Drugs use in haematology disorders in children, by Prof Godfrey Chan
- Use of cough and cold medicines in children by Prof Chun-Bong Chow
- Drugs and renal diseases in paediatrics by Prof Keith Lau
- Drugs use in Paeds ICU, a London's experience, by Ms Christina Leung, Clinical Pharmacist
- Medication safety in paediatrics, from a nursing perspective by Ms Winnie Lee, Consultant paeds nurse

Thank you

Any questions?