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Drug Use at Extremes of Age

LEARNING OBJECTIVES

- Paediatric dose estimation
- Paediatric use of antibiotics
- Drugs requiring dose modification in elderly
- Common ADRs in children
- Immunization schedule
- Prescribing cascade in elderly

PAEDIATRIC USE OF DRUGS

A child is not a little adult.

Paediatric definitions

- Premature neonate : <38 weeks gestation
- Newborn, neonate : Birth to 1 month old
- Infant, baby : 1 month to 1 year
- Young child : 2–5 years
- Older child : 6–12 years
- Adolescent : 13–18 years

Paediatric pharmacokinetics

(a) *Drug absorption*

- Neonates have potentially altered drug absorption as a result of decreased production of gastric acid that also decreases gastric emptying time.
- Those drugs that are absorbed in the stomach, by remaining in the stomach for an additional 6–8 hours may have enhanced effects as a result of increased absorption.
- Intestinal motility is reduced in neonates whereas, it is increased in infants and children.
- Intestinal surface area is reduced in neonates, near adult in infants and adult pattern in children.
- Effect of milk in the stomach can also influence oral absorption of drugs in neonates and infants.
- IM and percutaneous absorption is increased in infants and is of adult pattern in children.
- Rectal absorption is very efficient in neonates, efficient in infants and near adult pattern in children; rectal route is more reliable in neonates than the oral route.
- IV route is the best option to ensure adequate blood and tissue concentration; IM route

should be avoided as there is small muscle bulk and blood supply, absorption could be slow and erratic and the route is painful.

- There is significant systemic absorption across the skin surface; large skin surface area absorbs a lot of topical drugs especially from face and perineum.

(b) *Drug distribution*

- The infant has more body water and less fat than an adult as a percentage of total weight (85% water in premature neonate as compared to 60% in an adult); volume of distribution is therefore increased for water soluble drugs and decreased for lipid soluble drugs.
- Many drugs are less avidly bound to plasma proteins in neonates and plasma protein concentrations are also lower in neonates. This produces higher unbound fraction leading to increased clearance and diseased half-life; also increases toxicity.

(c) *Drug biotransformation*

- Elimination in the neonate is slower than in older children and adults. Biotransformation is reduced as the microsomal enzymes in the liver are immature; this results in prolonged half-life of drugs metabolised in liver.
- Drug doses should be adjusted for decreased hepatic clearance until a full-term newborn reaches 2 weeks.
- Bilirubin metabolic pathway (glucuronyl-transferase) is mature up to 1–2 weeks of age.

(d) *Drug excretion*

- Neonatal kidney function matures rapidly. At birth, a full-term newborn has approximately 33% of glomerular filtration rate and renal tubular excretion capacity of an adult. This capacity is 15% or less in premature infant.
- Doses of drugs dependent on renal excretion to a large degree (aminoglycosides, penicillins) must be adjusted in a neonate.

Paediatric pharmacodynamics

- CNS matures slowly and reaches adult levels at about 8 years of age. The blood–brain barrier is slow to develop enabling enhanced CNS effects with some drugs. Neonates are, therefore, sensitive to depressant effects of drugs such as phenobarbitone, morphine, chlorpromazine.
- CVS functions adequately in neonates and infants.
- Temperature regulating system is unstable and immature in neonates and infants. Many drugs cause wide fluctuations in temperature and have exaggerated responses in neonates and infants.
- Skin is more sensitive to drugs. Allergic reactions are common.

Paediatric dose estimations

One of the most difficult tasks in paediatric therapy is the calculation of dosage in children particularly in newborn babies, premature infants and very young children.

(a) Based on weight

(*i*) **Augsberger's rule:**

$$\text{Child's dose} = \frac{1.5 \times \text{weight in kg} + 10}{100} \times \text{Adult dose}$$

(*ii*) **Clarke's rule:**

$$\text{Child's dose} = \frac{\text{Weight in pounds}}{150} \times \text{Adult dose}$$

(b) Based on age

(*i*) **Young's rule:**

$$\text{Child's dose} = \frac{\text{Age in years}}{\text{Age} + 12} \times \text{Adult dose}$$

(*ii*) **Bruntoni's rule:**

Child's dose = 0.4 × Child's age next birthday in years x Adult dose

(*iii*) **Bastedo's rule:**

$$\text{Child's dose} = \frac{\text{Age in years} + 3}{30} \times \text{Adult dose}$$

(*iv*) **Cowling's rule:**

$$\text{Child's dose} = \frac{\text{Age at next birthday in years}}{24} \times \text{Adult dose}$$

(*v*) **Dilling's rule:**

$$\text{Child's dose} = \frac{\text{Age in years}}{20} \times \text{Adult dose}$$

(*vi*) **Augsberger's rule:**

$$\text{Child's dose} = \frac{4 \times \text{Age in years} + 20}{\text{Age} + 12} \times \text{Adult dose}$$

(*vii*) **Fried's rule for infants:**

$$\text{Infant dose} = \frac{\text{Age in months}}{150} \times \text{Adult dose}$$

(c) Based on surface area (SA)

(*i*) **Using nomograms:**
Read SA from a nomogram and then use the formula

$$\text{Child's dose} = \frac{\text{Surface area}}{1.73} \times \text{Adult dose}$$

(ii) Without nomograms:
A useful guide is as follows:

Weight (kg)	Surface area
10	0.5
20	0.75
30	1.0
40	1.25

Interpolate and extrapolate as necessary and use in the formula $\frac{\text{Surface area}}{1.73} \times$ Adult dose.

Common ADRs in children

- Skin reactions with sulfonamides, tetracyclines, penicillins, cephalosporins, INH, barbiturates, phenytoin, phenothiazines, narcotics, aspirin, indomethacin, iodides, griseofulvin.
- Growth retardation with tetracyclines, corticosteroids.
- Sexual precocity with androgens.
- Intracranial hypertension with corticosteroids, nalidixic acid, vitamins A and D, nitrofurantoin.
- Jaundice with sulfonamides, vitamin K.
- Bulging fontanelle, tooth staining with tetracyclines.
- Ototoxicity and deafness with aminoglycosides.
- Reye's syndrome in viral fever with aspirin.
- Gray baby syndrome with chloramphenicol.
- Juvenile arthropathy with fluoroquinolones.

Paediatric use of antibiotics

Preferred sites for IM injections

- Infants—upper anterolateral aspect of thigh.
- >2 years—ventrogluteal.
- Older children—deltoid.

Safety and efficacy (S/E)

- <12 years S/E not established—ampicillin-sulbactam, ticarcillin-clavulanic acid, piperacillin-tazobactam, cefditoren pivoxil, imipenem-cilastatin (IM).
- <8 years to be avoided—tetracyclines, fluoxetine.
- <9 months S/E not established—aztreonam
- <6 months S/E not established—cephalexin, cefprozil, ceftibuten, cefdinir, cefixime, azithromycin, cefpodoxime.
- <3 months S/E not established—cefuroxime axetil, nalidixic acid, atropine, emtricitabine, indomethacin, mefloquine, xylometazoline.
- <2 months S/E not established—sulfonamides, cefepime, cotrimoxazole.
- Not approved for children—cefoperazone, cefotetan, cefonicid, fluoroquinolones, tetracyclines (<8years).
- Not approved for neonates—ceftriaxone, piperacillin, cefaclor.

Immunization (Tables 78.1 and 78.2)

- All infants should be immunized except in these rare situations:
  (*a*) Anaphylaxis or severe hypersensitivity reaction.
  (*b*) BCG/yellow fever vaccine should not be given to an infant that exhibits signs and symptoms of AIDS.
- The following conditions are not contraindications for immunization:
  (*a*) Allergy or asthma (except known allergy to vaccine component).
  (*b*) Minor illness (RTI, diarrhoea).
  (*c*) Family history of convulsions or adverse effects during immunization.
  (*d*) Treatment with antibiotics.
  (*e*) Known/suspected HIV infection with no signs and symptoms of AIDS.

Table 78.1 Immunization schedule for infants recommended by the expanded programme on immunization

Vaccine	Birth	6 weeks	10 weeks	14 weeks	9 months
❑ BCG	✓				
❑ Oral polio	✓[1]	✓	✓	✓	
❑ DPT		✓	✓	✓	
❑ Hepatitis B[2]					
• Scheme A	✓	✓		✓	
• Scheme B .		✓	✓	✓	
❑ H-influenza type B		✓	✓	✓	
❑ Yellow fever[3]					✓
❑ Measles					✓

1. In polio-endemic countries
2. Scheme A: In countries where perinatal transmission of hepatitis B virus is frequent (Southeast Asia); Scheme B: In countries where perinatal transmission is less frequent (Subsaharan Africa).
3. In countries where yellow fever poses a risk.

(*f*) Signs and symptoms of AIDS (except BCG/yellow fever vaccine).
(*g*) Child being breastfed.
(*h*) Chronic diseases of heart, lungs, kidney, liver.
(*i*) Premature or low birth weight or infant with malnutrition.
(*j*) Recent or imminent surgery.

Important tips

- If a child has diarrhoea when you give oral polio vaccine administer an extra dose-fifth dose at least 4 weeks after he/she has received last dose in the schedule.
- If you are giving more than one vaccine do not use the same syringe and do not use the same arm or leg for more than one injection.
- Administer doses at correct intervals.

Table 78.2 Summary of vaccines

Vaccine	Route of administration	Injection site	Dosage
BCG	Intradermal	Outer upper left arm/shoulder	0.05 ml
DPT	Intramuscular	Outer mid thigh/outer upper arm	0.5 ml
Oral polio	Oral	Mouth	2 drops
Hepatitis B	Intramuscular	Outer mid thigh	0.5 ml
Measles	Subcutaneous	Upper left arm	0.5 ml
Yellow fever	Subcutaneous	Upper right arm	0.5 ml
Tetanus toxoid	Intramuscular	Outer upper arm	0.5 ml
H-influenza type B	Intramuscular	Outer mid thigh/outer upper arm	0.5 ml
Japanese encephalitis	Subcutaneous	Upper arm	0,5 ml, 1 ml (<3 years)
Meningococcal	Subcutaneous	Upper arm	0.5 ml

Table 78.3 Recommended doses in children of commonly used drugs

❑	Paracetamol	60 mg/kg/day	Divided 4–6 hourly
❑	Ibuprofen	40 mg/kg/day	Divided 6–8 hourly
❑	Mebendazole	100 mg/day	Pinworm 1 day; others bd for 3 days
❑	Amoxycillin	25–50 mg/kg/day	Divided 8 hourly
❑	Ampicillin	50–300 mg/kg/day	Divided 6 hourly
❑	Cephalexin	25–100 mg/kg/day	Divided 6 hourly
❑	Cefotaxime	100–200 mg/kg/day	Divided 4–6 hourly
❑	Erythromycin	20–50 mg/kg/day	Divided 6 hourly
❑	Gentamicin	2–7.5 mg/kg/day	Divided 8 hourly
❑	Promethazine	1–2 mg/kg/day	Divided 8 hourly
❑	Ondansetron	4 mg tds	
❑	Cefadroxil	30 mg/kg/day	2 doses, 12 hourly
❑	Cefixime	8 mg/kg/day	1–2 doses

GERIATRIC USE OF DRUGS

More than 90% of the elderly population (>65 years) receive drugs. Geriatric patients are not the same as younger population in their response. There are changes in kinetic and dynamic parameters which modify drug action

Why elderly have problems with drugs?

- ❑ Normal changes associated with aging cause senile bodies to handle drugs differently than young people.
- ❑ Confusion, fuelled by dementia, hearing or vision problems can lead to older patients not taking the right dose of their drugs or not taking them when and how they are supposed to.
- ❑ More drugs cause lower compliance and verbal instructions by the doctors are misunderstood.
- ❑ Elderly have more than one chronic illness, and need to take multiple drugs several times a day. More drugs cause more drug interactions.
- ❑ Sometimes, a drug that is used to treat one condition may make other conditions worse.

Geriatric pharmacokinetics

(*a*) *Drug absorption*

- ❑ There is increase in gastic pH and decrease in gastric motility, splanchnic blood flow and absorptive surface.
- ❑ The extent and rate of absorption is affected, but completeness of absorption is similar to that in younger patients; delay in onset of activity may occur.

(*b*) *Drug distribution*

- ❑ The elderly have decreased total body water, decreased lean body mass, decreased serum albumin concentration, increased α_1-acid glycoprotein concentration and increased proportion of body fat.
- ❑ The importance of increased free fraction of a drug due to decrease in albumin binding is questionable because while additional free drug is available for receptor binding, more free drug is also available for metabolism and elimination.

(*c*) *Drug biotransformation*

- ❑ There is decrease in hepatic mass and hepatic blood flow; hepatic clearance of some drug may be impaired.
- ❑ Half-life is often prolonged in the elderly; longer t½ means that time to steady state is longer, drug elimination takes longer and dose intervals may be longer.

(*d*) *Drug excretion*

- ❑ There is decrease in renal blood flow, glomerular filtration rate and tubular secretion.

- Even in the absence of kidney disease, renal clearance may be decreased by 35–50% in elderly patients; dose adjustments are required for drugs eliminated mainly by the kidneys.

Geriatric Pharmacodynamics

- Homeostatic adaptation is less efficient and target organ sensitivity may be altered in the elderly.
- Homeostatic responses tend to be blunted-orthostatic hypotension is more pronounced due to reduced ability of the baroreceptors to compensate for changes in blood pressure.
- Drug sensitivity is altered—increased analgesic effect of opioids, increased sedation from benzodiazepines and other CNS depressants, increased risk of bleeding during the use of anticoagulants.
- Alterations in receptor function may occur with age leading to impairment of adenergic and cholinergic functions.

ADRs in elderly

- It is estimated that 30% of elderly patients on treatment suffer from ADRs in contrast to 10% of patients aged 20–30 years. Reasons for high frequency of ADRs are:
- Multiple chronic diseases being treated with potent, multidrug therapy.
- Age-related changes in kinetics and dynamics which alter drug response.
- Inappropriate and irregular self medication.
- Multiple independent consultations leading to overlap of therapeutic drugs.
- Ignorance and negligence about ADRs.
- Non-compliance with prescription drugs.
- Lack of education about over the counter drug use.

Prescribing cascade

- Begins when any ADR is misinterpreted as a new disorder. In response another drug is prescribed and patients develop additional ADR related to the second drug.
- Prescribers should always consider the possibility that a new symptom or sign is due to drug therapy.
- Commonest cause of polypharmacy in the elderly:

(a) NSAIDs → Hypertension → Antihypertensive therapy.
(b) Metoclopramide → Parkinsonism → L-dopa.
(c) Amlodipine → Oedema → Furosemide.
(d) NSAIDs → Gastritis → Ranitidine → Delirium → Haloperidol.
(e) Hydrochlorothiazide → Gout → NSAID →Hypertension → Losartan.

Drugs and cognitive impairment

- Drugs are a common cause of potentially reversible cognitive impairment in the elderly.
- Demented patients are particularly prone to delirium from drugs.
- Anticholinergic drugs are common offenders.
- Cimetidine, steroids and NSAIDs are also responsible.

Table 78.4 Drugs requiring dosage modifications in the elderly

Prazosin	Calcium blockers	Antiarrhythmics	Theophylline
Digoxin	ACE inhibitors	Aminoglycosides	Cephalosporins
Penicillins	Carbamazepine	Chlorpropamide	Metformin
L-dopa	Phenothiazines	Pancuronium	Zolpidem
Phenytoin	Benzodiazepines	Venlafaxine	Pethidine
Lithium	Risperidone	Metoclopramide	Thyroxine
Warfarin	Atenolol	Cimetidine	TCAs

Drugs and falls

- Falls are very common in elderly and drugs are often the offenders.
- Biggest risk drugs are long-acting benzodiazepines and other sedative-hypnotics.
- Both SSRI and TCA are associated with increased risk of falling.
- There is a mild risk of falls from diuretics, digoxin and class 1A antiarrhythmics.
- β-blockers are not associated with increased risk of falling and are wrongly implicated.

Enhancing compliance in elderly

It is especially useful in the elderly to follow the rule for enhancing compliance. Economy in the use of drugs, single-dose regimens, once or twice daily dosing, clear instructions and the use of compliance aids can enhance the therapeutics. Compliance aids include cards listing all the drugs with their time of intake, patient information leaflets and unit dose packaging.

General guidelines for prescribing in elderly

- Consider dose reduction in patients over 55 years.
- Start low, go slow for metabolised drugs.
- Aim for once or twice daily dosing.
- Monitor more frequently, especially for drugs with a low therapeutic index.
- Use as few drugs as possible.
- Do not prescribe a drug with major adverse effect.
- Rational FDCs may be used if appropriate, as they improve compliance.
- Think about ADRs if new symptoms appear after drug therapy.

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FIND OUT

1. When can the booster be given after the first dose of hepatitis A vaccine?
2. What is the duration of immunity following 3 doses of hepatitis B vaccine?
3. Which β-blockers do not appear to change their clearance pattern with age?