لجنة الطب والجراحة

No.5

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Pharmacology Sheet

DOCTOR:

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Drug Prescribing in Infants, Children and Elderly

Intro:

- Less doses are needed in young children and elderly than in an adult due to changes in:
  1. Drug pharmacokinetics
  2. Sometimes pharmacodynamics
- We compare those 3 groups with healthy adults (no physiological diseases) to determine the changes that will take place in terms of drugs choices and doses.
- Children should not be regarded as small adults when prescribing for them, particularly in the first few months of life. They differ in:
  1. Body composition. E.g. we cannot give children lipid soluble drugs like adults because they do not have the same fat composition.
  2. Elimination of drugs.
- Determinants like body weight, age and surface area are used to choose the proper infants/ children drug doses based on ALL pharmacokinetics and SOME pharmacodynamics factors.
- Infants and children are mostly composed of water with lower fat compositions than adults.
- Generally, in those 3 sensitive groups we should not give a drug that is only eliminated by one organ system e.g. kidney or liver, because it may strain this organ and cause permanent irreversible damage.

Infants (1-12 months) and Children (1- 12 years):

- Drugs responses may differ from adults due to:
  1. Surface area/ body weight ratio is less in neonates (under 1 month).
  2. Pharmacokinetics changes:
     - ***Absorption:***
       - GI Absorption is variable (not constant, it changes contrary to the stable GI absorption in adults) e.g. it is normal for diazepam (it calms [relaxes] brain and nerves, -> used before surgeries and c section deliveries as well as for muscle spasms) and digoxin. For ampicillin, flucloxacillin and amoxicillin is greater in neonates due to decreased gastric acidity. For paracetamol, it is reduced (a commonly used drug for analgesia [pain relieve] and fever, if it is used in greater doses than recommended, it may lead to irreversible liver damage).
       - Percutaneous absorption increases due to skin hydration (or hydratation; due to lower fat composition) and thin keratin layer (e.g. for steroid creams).
       - Parenteral injections: absorption is slower after IM injection due to small muscle mass and decreased fat.

Summary*:*

- Prolonged gastric emptying time and irregular gut motility.

- Reduced trans time in upper intestine.
- Presence of food decreases absorption of ampicillin and penicillin. (two antibiotics, that why they should be taken before meals -> "ante cibum" or more commonly "AC").
- Absorption of lipid soluble drugs is reduced in infants as they have low concentrations of lipase and acid -> look for water soluble drugs to use rather than lipid soluble ones.
- The decrease in gastric acidity will facilitate the absorption of some drugs.

- ***Distribution:***
  - Total body water is more than in adults and is mostly extracellular, so increased Vd (volume of distribution) of water-soluble drugs
  - Fat content is lower in children, so decreased Vd for lipid soluble drugs (e.g. diazepam)
  - GI function: gastric emptying time is more while gastric acid output is less in neonate than in adults (variable absorption).
  - Plasma protein binding is reduced in neonate due to lower albumin concentration and altered binding capacity, so concentration of free active fraction is increased (highly bound drugs e.g.: phenytoin -> anti-epileptic). So, due to the increase in free drugs concentration (the ones responsible for exerting the physiological action) -> lower doses should be given. We should follow up with the patient and monitor their response all the time.
  - BBB (Blood Brain Barrier) is more permeable in neonate and children (because it has not developed fully yet, it is completely developed after 5 weeks of delivery [make sure: is it weeks or months?]) leading to increased risk of drug penetration to the CNS (more concentrations of the lipid soluble drugs will cross the barrier -> accumulation happens -> toxicity).
  - Example:
    - Lipid soluble drugs. (Propranolol: has the ability to pass through breast milk -> may cause hypotension in infants)
    - Morphine -> if high levels reached the brain -> CNS depression will occur (will be discussed more later).

- ***Excretion:***
  - Renal clearance is less efficient, so t ½ of drugs eliminated mainly by kidney is prolonged (e.g. ampicillin and digoxin). Adult glomerular filtration rate is attained after 3-5 months; adult secretory and reabsorptive capacity is attained after 7 months (e.g.: aminoglycosides, and diuretics are cleared from the body very slowly in the first weeks of like).
  - In older children drug elimination by metabolism or renal excretion is faster than in adults, so t ½ of drugs is shortened.

- ***Metabolism:***

- Hepatic enzyme activity is low in neonate for some drugs, this would increase t ½ of drugs eliminated by liver. (It takes longer times for elimination to complete).
- Hepatic microsomal enzyme system (CYP450 is ONE of them and the most affected one) is relatively immature in infants in the first 4 weeks after birth.
- Hepatic drug metabolism increases in older infants and children (e.g. phenobarbitone metabolism is faster in children than adults). (older infants' and children's livers are still healthy compared to adults' livers who have already been damaged by drug abuse, alcohol … etc -> infants' and children's livers metabolizes faster.
- Note that if our bodies want to get rid of lipid soluble drugs, the body must convert it into water soluble drugs first. As most if not all of the drugs given to children are water soluble, this thing does not really apply on them.

- The third reason behind the difference in drug responses in infants and children from adults will be:

3. Changes in pharmacodynamic:
   - Nothing is set on stone here, depending on the type of receptor we are dealing with, the mechanism of action occurs (either inhibition or stimulation).
   - Increased sensitivity to CNS depressants (e.g. morphine). (the sensitivity increases with the increase in numbers of receptors involved).
   - Heart is more tolerant to digoxin toxicity.
   - Hyperkinesia (extensively excessive movements or simply hyperactivity) with phenobarbitone.
   - Sedation of hyperactive children with amphetamine.

Dose Calculation:

- Clark's rule:
  - Child dose= adult dose x child BW (kg)/ 70kg
  - BW: body weight in Kg
  - Why 70 kg exactly? It is the reference average of adult body weight.

- Young's rule:
  - Child dose= adult dose x child age (years)/ (age+12)

- Calculation based in BW or age tend to underdose the child

- Determination of drug dosage from surface area (SA): (most commonly used approach)
  - Child dose= adult dose x SA child (M^2)/ 1.8
  - SA: surface area (in square meters)

BW (Kg)	Age	SA(M^2)	% adult dose
3	Newborn	0.2	12
6	3months	0.3	18
10	1 year	0.45	28
20	5.5 years	0.8	48
30	9 years	1	60
40	12 years	1.3	78
50	14 years	1.5	90
60	Adult	1.72	100
70	Adult	1.76	103

**** this table is not to be memorized, it will be given in the exam, if needed.**

Children's Prescription Writing:

- **Age is a legal requirement in the case of drug prescription for children under 12 years of age (preferable to stage the age for all prescriptions). -> knowing the age helps in knowing the preferred route of administration to use. E.g. a 2 years old child can not swallow -> do not consider tablets nor capsules.**
- **To stage the strengths of capsule and tablets is very important. Liquid preparations sugar- free are better for children (reduce dental decay).**
- **Parents should be advised not to add any medicine to the infant's feed (may interact).**
- **Parents must be warned to keep all medicine out of reach of children.**
- **Avoid prolonged treatment that have delayed complications (e.g. steroids).**
- **Use suitable dosage forms (e.g. those with shorter durations, lower adverse effects, faster therapeutic effects, better tastes, more accessible, easier to administer [easy to swallow] … etc).**

Drugs and the Elderly:

- **Drugs response in the elderly differ from adults due to:**
  1. **Reduced muscle mass and body weight.**
  2. **Changes in pharmacokinetics:**
     - ***Absorption:***
       - **Reduce gastric acid secretion, delayed gastric emptying and reduced gut motility and blood flow, increased incidence of duodenal diverticula (a pouch attached to the duodenum, the 1st one of the small intestine) and bacterial over growth resulting in malabsorption, but in general no major effect on absorption from intestine (e.g.: reduced absorption of iron, calcium, thiamine (vitamin B1), xylose, and galactose (all need active transport mechanisms).**
       - **Generally, absorption happens in the upper small intestine.**
     - ***Distribution:***

- Reduce total body water, so decreased Vd of water-soluble drugs; so, lower doses are required for lithium and digoxin.
- Relative increase in fat, so increased Vd of lipid soluble drugs (e.g. benzodiazepines, lignocaine (local anesthetic), gentamycin, morphine, tolbutamide).
- Decreased albumin (increases the unbound fraction of highly protein binding drugs like lidocaine, and propranolol and increased gamma globulins (for acidic drugs; e.g. warfarin, phenytoin and digoxin).
- Elderly have higher fat composition and lower total body water than adults. So, the exact opposite of children and infants.

- ***Metabolism:***
  - The (1) use of alcohol and (2) medications (especially in those using polypharmacy [regular 5 or more drugs]) and (3) the long-term exposure to environmental toxins and (4) malnutrition lead to decreased hepatic blood flow and reduced capacity for microsomal enzyme induction, and decreased ability of liver to recover from injury.
  - Polypharmacy may also decrease the glomerular filtration rate [GFR] (i.e. kidney function).
  - Thus, t ½ of drugs mainly eliminated by liver is prolonged (e.g.: diazepam, quinidine, theophylline, propranolol, nortriptyline).
- ***Excretion:***
  - Decreased glomerular filtration rate and tubular secretion, so t ½ of drugs mainly eliminated by kidney is prolonged (e.g.: aminoglycosides, digoxin, lithium, methotrexate (anti-cancer medication), procainamide, tetracycline, penicillin(s), cephazolin)
  - Note: serum creatinine remains normal due to decrease in its production as a result of decrease in skeletal muscle mass.

- The rest of the reasons behind the difference in drug responses between elderly and adults will be:

3. Changes in pharmacodynamic:
   - Age- related impairment of baroreceptor reflex (decreased response).
   - Organ sensitivity: certain systems more sensitive to drug action.
   - Brain function is easily disturbed (hypnotic and other centrally acting drugs can easily produce confusion and excessive drowsiness). The control of blood pressure is more easily disturbed, causing fainting. Increased sensitivity to digoxin (will have higher affinity to receptors).
   - Note: all these pharmacodynamic changes might be due to receptor changes (e.g. a reduction in receptors numbers -> a reduction in receptors sensitivity to drugs), kinetic changes and impaired homeostatic reflexes especially in CVS.
   - CVS (specifically the heart) has muscarinic and adrenergic receptors. Among the adrenergic ones there is alpha 1, beta 1 and beta 2. Beta 1 receptors have

higher affinity for norepinephrine (noradrenaline) than Beta 2 receptors while both of them have almost the same affinity for epinephrine (adrenaline). Beta blockers mostly work on those specific receptors. Changes in those receptors characteristics may lead to changes in drug responses.

4. Compliance may be poor due to complicated drug regimes or polypharmacy may be impossible for elderly to follow so they either give up taking their drugs or take the wrong doses at the wrong times.

5. Adverse reactions: are very common in elderly than in younger due to:
   - Often need several drugs at the same time.
   - The elimination of drugs is impaired so that they are exposed to higher concentrations on the body (unless the doses are suitably adjusted).
   - Are often severely ill and this may interfere with elimination.
   - Drugs associated with adverse reactions (digoxin, diuretics, NSAIDS, hypotensive(s), centrally acting agents) are often prescribed for elderly.

General Principles When Using Drugs in Elderly:

- A full drug history is important as the patient may have experienced an adverse effect from a drug in the past. Medication already being taken may raise the possibility of an interaction.
- Keep the regime simple -> do not give lots of drugs, give the most effective ones with the lowest possible adverse drug reactions.
- Prescribe the smallest effective dose (so you can easily stop the medication if any side effects emerged, e.g. some patients may not tolerate the hyperglycemia associated with beta blockers when used for hypertension [beta blocker goes to pancreas and blocks insulin]), if possible, use drugs which are short- acting.
- Do not continue to use a drug for longer than necessary.
- If the condition of the patient is deteriorating, remember that a drug may be responsible.
- Elixirs (liquid dosage form) may be easier than tablets.
- Clear and simple instructions.

يظنّ الإنسان..

في ظلّ هذه الأحداث، أن تركهُ الذّنب وضبطهُ لنفسه وتحسينه قلبه لن يساهم في نصرة أمّته بشيء، وأنه واحد لا عَدّ له ولا تأثير، وينسى أن الأمر عائد له بالأصل، لقلبه وروحه وجسده وحياته، ينتصر على شهوته وهواه، ويكون مستعدًا للرباط على ثغرٍ يتم فيه دوره؛ إعداد اليوم، ثغور الغد.

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