Complications and effects associated with medications usage in pediatric patients

Objectives

- **TO KNOW COMPLICATIONS AND EFFECTS ASSOCIATED WITH MEDICATIONS USAGE IN PEDIATRIC PATIENTS .**
- **TO KNOW Pharmacokinetics: neonate & infant.**
- **To know Hepatic metabolism**
- **To know Adverse drug reactions**

DRUG THERAPY FOR PEDIATRIC PATIENTS

- Pediatrics covers all pts

  under the age of 16 years
- Pediatric pts in different age groups present different therapeutic challenges.
- Pediatric pts respond differently to drugs than the rest of the population

Pediatric pts are more sensitive to drugs than other pts, & they show greater individual variation.

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WHY?

- Drug sensitivity in the very young results largely from **Organ System Immaturity** ⇨ the result is increased risk of adverse drug reaction.

PEDIATRIC DRUG THERAPY IS MADE EVEN MORE DIFFICULT BY

INSUFFICIENT DRUG INFORMATION.

Until recently, the Food & Drug Administration (FDA) did not require drug trials in children.

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As a result, for many drugs given to young pts we lack good information on dosing, pharmacokinetics, & the effects, both therapeutic & adverse.

Despite lack of good information, the clinician must nonetheless use drugs to treat Pediatric pts. → The clinician must try to balance benefits versus risks, without knowing with precision what the benefits & risks really are.

Pharmacokinetics: neonate & infant

Pharmacokinetic factors determine the concentration of a drug at its sites of action, & hence determine the intensity & duration of responses.

- If drug levels are elevated responses will be more intense.
- If drug elimination is delayed, response will be prolonged.

- Because the organ systems that regulate drug levels are not fully developed in the very young pts, ⇨
- these pts are at risk of both possibilities: drug effects that are unusually intense & prolonged.
- By **accounting for pharmacokinetic** differences in the very young pts, we can **↑ the chances that drug therapy will be both effective & safe.**

- What is the major reason for increase drug sensitivity in infants?

- The increased sensitivity of the infants is **due largely to the immature state of five pharmacokinetics processes**:
- ❶ drug absorption,
- ❷ renal drug excretion,
- ❸ hepatic drug metabolism,
- ❹ protein binding of drugs, &
- ❺ exclusion of drugs from the CNS by the blood brain barrier.

Drug absorption:

- ***Oral administration***:
- G.I. physiology in the infant is very different from that in the adult. As a result, drug absorption may be enhanced or impeded, depending on the physicochemical properties of the drug involved.

- Gastric emptying time:
- is prolonged & Irregular in early infancy, & then gradually reaches adult values by 6 – 8 months.
- For drugs that are absorbed primarily from stomach, delayed gastric emptying enhances absorption.
- On the other hand, for drugs that are absorption primarily from intestine, absorption is delayed.
- Because gastric emptying time is irregular, the precise affect on absorption is not predictable.

- Gastric acidity is very low 24 hrs after birth & does not reach adult values for 2 years. Because of low acidity, absorption of acid-labile drugs is increased.

- *Intramuscular administration*: drug absorption following IM injection in the neonate is slow & erratic. Why?
- Delayed absorption is due in part to low blood flow through muscle during the 1st days of postnatal life. By early infancy absorption of IM drugs become more rapid than in neonates & adult.

- **QQ: If intramuscular injections are required in infants, we use the thigh muscles. Why?**

- *Percutaneous absorption* ⇨ because skin of the very young pts is thin percutaneous drug absorption is significantly greater than in older children & adults. This increases the risk of toxicity from topical drugs.

Drug distribution:

- *Protein binding*: binding of drugs to albumin & other plasma proteins is limited in the infant. This is because
- ❶ the amount of albumin is relatively low
- ❷ endogenous compounds (e.g. fatty acid, bilirubin) compete with drugs for available binding sites. Consequently, drugs that ordinarily undergo extensive Protein binding in adults undergo much less binding in infants.

- As a result, the concentration of free levels of such drugs is relatively high in the infant, thereby intensifying effects.
- To ensure that effects are not too intense, dosages in infants should be reduced. Protein-binding capacity reaches adult values within 10 –12 months.

- Blood-brain barrier: the BBB is not fully developed at birth. As a result, drugs & other chemicals have relatively easy access to the CNS, making the infant especially sensitive to drugs that affect CNS function. Accordingly, all medicines employed for their CNS effects (e.g. morphine, Phenobarbital) should be given in reduced dosage. Dosage should also be reduced for drugs used for actions outside the CNS if those drugs are capable of producing CNS toxicity as a side effect.

Hepatic metabolism:

- The drug-metabolizing capacity of newborns is low. As a result, neonates are especially sensitive to drugs that are eliminated primarily by hepatic metabolism. When these drugs are used, dosages must be reduced. The capacity of the liver to metabolize many drugs increases rapidly about 1 month after birth, & approaches adult levels a few months later. Complete maturation of the liver develops by 1 year.

Renal excretion

- Renal drug excretion is significantly reduced at birth. Renal blood flow, glomerular filtration, & active tubular secretion are all low during infancy. Because the drug-excreting capacity of infants is limited, drugs that are eliminated primarily by renal excretion must be given in reduced dosage. Adult levels of renal function are achieved by 1 year.

Pharmacokinetics: children 1 year and older

- By the age of 1 year, most pharmacokinetic parameters are similar to those in adults. Hence, drug sensitivity in children over the age of 1 year is more like that of adults than of the very young.

- Although pharmacokinetically similar to adults, children do differ in one important way:
- *they metabolize drugs faster than adults do.*

Drug-metabolizing capacity is markedly elevated until the age of 2 years, & then gradually declines. A further sharp reduction takes place at puberty, when adult values are reached.

- Because of enhanced drug metabolism in children, an increase in dosage or a reduction in dosing interval may be needed for drugs that are eliminated by hepatic metabolism.

Adverse drug reactions

- Like adult, pediatric pts are subject to adverse reactions when drug levels rise too high. In addition to these dose-related reactions, pediatric pts are vulnerable to unique adverse effects related to immature state of organ systems & to ongoing growth & development.

- **Adverse Drug Reactions Unique to Pediatric Patients**
- **Androgens**
- Premature puberty in males; reduced adult height from premature epiphyseal closure
- **Aspirin &other Salicylates**
- Severe intoxication from acute overdose (acidosis, hyperthermia respiratory depression); Raye's syndrome in children with chickenpox or influenza
- **Chloramphenicol**
- Gray syndrome (neonate & infant)
- **Glucocorticoids**
- Growth suppression with prolong use
- **Fluroquinolones**
- Tendon rupture
- **Hexachlorophene**
- CNS toxicity (infant)
- **Nalidixic acid**
- Cartilage erosion
- **Phenothiazines**
- Sudden infant death syndrome
- **Sulfonamides**
- Kernicterus (neonate)
- **Tetracycline**
- Staining of developing teeth.

Dosage determination

- Pediatric doses have been established for some drugs but not for others. For drugs that do not have an established pediatric dose, dosage can be extrapolated from adult doses. The following methods are used for these calculations:

- The method of conversion employed most commonly is based on body surface area:⇨ Use the estimated body surface area in the following formula to calculate the child's dose:

  child's dose = body surface area /1.73 m^2 X Adult dose

- This method is considered a more accurate method than those based on other characteristics. Body surface area, based on height and weight, is estimated using a nomogram

- Another method : Clark's rule is based on weight and is used for children at least 2 years of age:

  child's dose = weight in pounds / 150 X Adult dose

Please note that initial pediatric dose – whether based on established pediatric dose, or extrapolated from adult doses – are at best an approximation. Subsequent doses must be adjusted based on clinical outcome & plasma drug concentrations. These adjustments are especially important in neonates & young infants. Clearly, if dosage adjustments are to be optimal, it is essential that we monitor the pt for therapeutic & adverse responses.

Q uestions

- W hat is the major reason for increase drug sensitivity in infants?

THANK YOU