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"Posology: How medicinal formulation dosed"

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ABSTRACT: The dosage of drugs which might be used in children must be determined to avoid empirical use, even when no application has been submitted for a paediatric licence. Toxicological evaluation and assessment of the effects on growth, an adapted pharmaceutical form and paediatric pharmacokinetic and adult clinical data are essential before conducting trials designed to determine the paediatric dosage.
The dose used during preliminary studies is extrapolated from the adult dose expressed in relation to weight, tested in a dose-effect study, and then more accurately defined on the basis of pharmacokinetic data in different age groups. Obtaining consent from both parents for studies whose direct benefit is not always obvious, as well as the global cost of these studies, constitute drawbacks to paediatric drug development.
Incentives to determine a paediatric dosage could consist of public participation in funding, prolongation of the patent, and granting an advantageous price for a specifically paediatric pharmaceutical form or indication.

I. INTRODUCTION:

It is not enough to simply tailor information available in adults to fit children. In the not- too- distant past, the use of Clark's rule and other formulae assumed children were small or young adults and scaled accordingly.

Doses for children were determined by multiplying the adult dose by the ratio of the child's weight to 150 pounds, for example. Studies to verify that doses so calculated were appropriate, safe, and effective were rarely conducted, in part because of the hesitancy to subject children to the demands of participation in clinical trials.

Information about the stability, palatability, or acceptability of either the commercially available or extemporaneously prepared dosage forms was limited. Unfortunately, we have learned from therapeutic misadventure that pediatric- specific pharmacokinetic, safety, and efficacy data must be collected across the age and developmental spectrum so that clinicians can use medication optimally and avoid potentially severe adverse reactions.

It is useful to consider an example to understand why pediatric subjects must be included in drug development. Chloramphenicol at doses of 100 mg/kg/day in divided doses was administered to neonates to treat or prevent infections in hospital nurses .

Cases were reported of babies who had been treated for 3 or 4 days and were then observed to have abdominal distention with or without emesis, progressive pallid cyanosis, and vasomotor collapse, frequently accompanied by irregular respiration and who sometimes died with a few hours of onset of distress.

The collection of symptoms was referred to as gray syndrome because of the ashen appearance of the skin. Assay of 200- µL blood samples, collected using finger- and heel- sticks, in affected infants showed their chloramphenicol concentrations to be unusually high.

A series of focused clinical studies subsequently conducted in groups of 3 to 5 patients showed greatly prolonged half- lives (26 hours) in the very young children who were 1 to 2 days of age, compared with half- lives of 10 hours in babies who were 10 to 16 days of age. Ultimately, it was determined that slow conversion of chloramphenicol to metabolites and immature renal tubular excretion were likely responsible for the high concentrations.

It was subsequently recommended that full- term infants receive 50 mg/kg/day and premature infants receive 25 mg/kg/day for the first week of life. The report summarizing the investigation,[2] published almost 60 years ago, encapsulates solutions to many of the challenges of determining the best dose in young infants and

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even recommends the use of therapeutic drug monitoring for prolonged therapy.

It is now expected that medications come to market with directions for safe and effective use for patients of all ages or, alternatively, with statements that use in certain age ranges is not indicated for the approved indications. The directions, including contraindications and cautions, should be based on data collected in appropriately designed studies or robust documentation from epidemiological and toxicology studies.

It is unfortunate that previous hesitancy to include children in clinical trials has resulted in gaps in the information available. Current drug development practices will hopefully make these deficiencies a thing of the past.

If we agree that all drugs that are developed should include children of all ages in clinical trials, let us first look at the drug development process in general. The potential list of pharmaceutical products that could be developed is almost endless. With thousands of diseases already described, continuing investigation into pathophysiology and identification of potential targets that could be manipulated to remediate or even cure and huge expansion of types of medicines that can be synthesized, there is a very long list of potential products that could be developed. Choices about which particular projects to advance are based on many factors.

What therapeutic areas is the sponsor (company, manufacturer) of the development project already working in. It is easier to develop and market products to an existing community. What are the largest threats to public health or well- being that demand immediate attention and are likely to be supported by payers? Big, messy problems, such as Alzheimer's disease, may be solved more readily if there are many different sponsors working on the problem. Ongoing collaboration between academic researchers and private industry may also suggest emphasis on particular diseases.

Drug development begins with the end in mind, by making a mockup of what would be the ideal product labeling, including the indication, posology for all age groups, and the anticipated adverse reactions and precautions required for the most effective and safe use. With ideal product labeling outlined, a development plan is prepared that includes all the clinical and nonclinical studies required to provide information needed to support the specific language in the label.

Each discipline, including discovery, clinical and nonclinical pharmacology, clinical and medical research, product formulation, toxicology, safety and epidemiology, among other functions, then expands its portion of the development plan to assess what is already known about the new chemical entity and what studies need to be performed to gather new information required either for the label itself or by other disciplines, so that they may perform their studies. Drug development is highly regulated, and so the data required for approval and, in turn, the studies required to provide much of the data are described in regulatory guidance statements and regulations, including the definition of a child.

DEFINATION OF POSOLOGY :

"The branch of pharmacology dealing with the determination of dosage".

Posology: (Derived from the greek : Posos-how much, and logos- science) is the branch of **pharmacology** dealing with doses. Dose: ... in a particular patient with the lowest possible dose.

"Posology is branch of pharmacy and more specifically pharmacology which deals with calculation of dose of drugs".

Posology includes calculation of dose of drug depending on following factors:

- Age (neonates, paediatric, adult, geriatric)
- Sex (Male, Female)
- Body surface area (varies with age of person)
- Body weight (varies with age of person)
- Route of administration .

‘‘The study of the dosages of drugs, especially the determination of appropriate dosages.

FACTORS AFFECTING POSOLOGY :

- Age
- Sex.
- Body weight
- Route of administration
- Time of administration
- Environmental factors
- Emotional factors
- Presence of diseases
- Accumulation
- Additive effects
- Synergism
- Antagonism
- Idiosyncrasy
- Tolerance
- Tachyphylaxis

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- Metabolic disturbance.

1. AGE :

The pharmacokinetics of many drugs changes with age. - Newborn infants (pediatric) are abnormally sensitive to certain drugs because of the immature state of their hepatic and renal function by which drugs are inactivated and eliminated from the body. Failure to detoxify and eliminate drugs results in their accumulation in the tissues to a toxic level.

- Whereas, elderly patients are more sensitive to some drug effect e.g. hypnotics which may produce confusion state in them.

2. SEX :

Women do not always respond to the action of drug in the same manner as it done in men. Special care should be taken when drugs are administered during menstruation, pregnancy & lactation. The strong purgative eg. Aloes should be avoided during menstruation. Similarly the drugs which may stimulate the uterine smooth muscles e.g. drastic purgative, antimalarial drugs, ergot alkaloids are contra indicated during pregnancy. - Alcohol, barbiturate, narcotic drugs acts on foetus through placenta. During lactation, morphine, tetracycline avoided because its affect on babies.:

- Women are more susceptible to the effects of certain drugs than are men.
- On the basis of body weight female adults generally requires smaller doses than males.
- Because % of adipose tissue is greater and % of water is lower in adult females as compared to adult males.
- Pregnant women and nursing mothers should use medications only with the advise and under the guidance of their physician.

3. BODY WEIGHT :

The average dose is mentioned either in terms of mg per kg body weight. Another technique used as a total single for an adult weighing between 50-100kg. However, the dose expressed in this fashion may not apply in case of obese patients, children & malnourished patients. It should be calculated according to body weight

4. ROUTE OF ADMINISTRATION :

I.V doses of drug are usually smaller than the oral doses. Intravenous route this might enhance the chances of drug toxicity. The effectiveness of drug formulation is generally controlled by the route of administration.

5. TIME OF ADMINISTARTION :

The presence of food in the stomach delay the absorption of drug & rapidly absorbed from the empty stomach. But it does not mean that much effective when taken during or after meal. Iron, arsenic & cod-liver oil should be given after meal & antacid drugs taken before meal.

6. ENVIROMENTAL FACTORS :

The personality & behavior of a physician may influence the effect of drug especially the drugs which are intended for use in a psychosomatic disorders. The females are more emotional than male & required less dose of certain drugs. Inert dosage forms called placebos which resemble the actual medicament in the physical properties are known to produce therapeutic benefit in disease like angina pectoris & bronchial asthma.

7. PRESENCE OF DISEASE :

Drugs like barbiturates & chlorpromazine may produce unusually prolonged effect in patient having liver cirrhosis. Such as, streptomycin produce toxic effect on these patient their kidney function is not working properly because streptomycin excreted through kidney.

8. ACCUMULATION :

Some drugs produces the toxic effect if it is repeatedly administered for long time e.g. digitalis, emetine, heavy metals because these drugs excreted slowly. This occurs due to accumulative effect of the drug.

9. ADDITIVE EFFECT :

When two or more drugs administered together is equivalent to sum of their individual pharmacological action, the phenomenon is called as additive effect. E.g ephedrine & aminophylline in the treatment of bronchial ashtma.

10. SYNERGISM :

When desired therapeutic result needed is difficult to achieve with single drug at that time two or more drugs are used in the combination form for increasing their action this phenomenon is called synergism.

- When 2 or more drugs used in combination, then total pharmacological action is the combination is increased.
- It is useful when desired therapeutic result needed is to achieve with a single drug.

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- Ex. Procaine and Adrenaline combination increases theduration of action of Procaine.

11. ANTOGONISM:

When the action of one drug is opposed by the other drug on the same physiological system is known as drug antagonism. The use of antagonistic response to drugs is valuable in the treatment of poisoning. E.g. milk of magnesia is given in acid poisoning where alkaline effect of milk of magnesia neutralise the effect of acid poisoning. When adrenaline & acetylcholine are given together, they neutralise the effect of each other due to antagonism because adrenaline is vasoconstrictor & acetylcholine is vasodilator.

12. IDIOSYNCRACY :

Idiosyncrasy is also called as allergy. An extraordinary response to a drug which is different from its characteristic pharmacological action is called idiosyncrasy. E.g. small quty. of aspirin may cause gastric hemorrhage. E.g some persons are sensitive to penicillin & sulphonamide because they produce severe toxic effect.

13. TOLERANCE :

When an unusually large dose of a drug is required to elicit an affect ordinarily produced by the normal therapeutic dose of the drug, the phenomenon is called as drug tolerance. E.g. smokers can tolerate nicotine, alcoholic can tolerate large quantity of alcohol. The drug tolerance is of two types: True tolerance, which is produced by oral & parenteral administration of the drug. Pseudo tolerance, which is produced only to the oral route of administration.

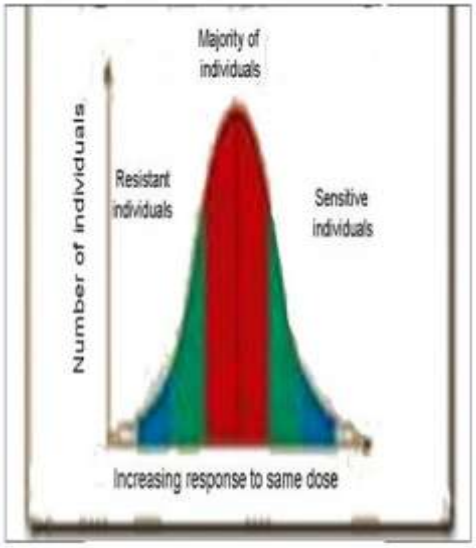
14. TACHYPHYLAXIS :

When some drugs administered repeatedly at short intervals, the cell receptors get blocked up & pharmacological response to that drug decreased. The decreased response cannot be reversed by increasing the dose this phenomenon is called tachyphylaxis or acute tolerance. - E.g. ephedrine given repeated dose at short intervals in the treatment of bronchial asthma may produce very less response due to tachyphylaxis.

15. METABOLIC DISTURANCE :

Changes in water electrolyte balance & acid base balance, body temperature & other physiological factor may modify the effect of drug. E.g. salicylates reduce body temperature in only in case an individual has rise in body temperature. They have no antipyretic effect if the body temperature is normal.

Dose – Response curve :



Drug effect in a population sample
(Dose – response curve)

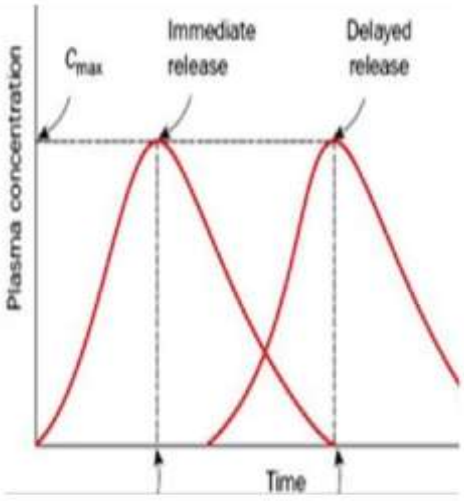


Fig : Plasma concentration vs time

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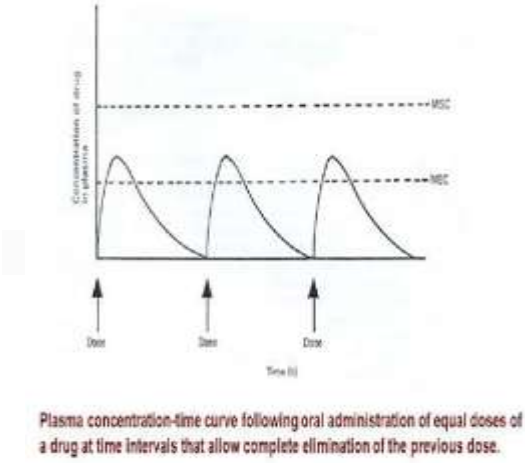

Plasma concentration-time curve following oral administration of equal doses of a drug at time intervals that allow complete elimination of the previous dose.

Fig : Concentration of drug in plasma vs Time

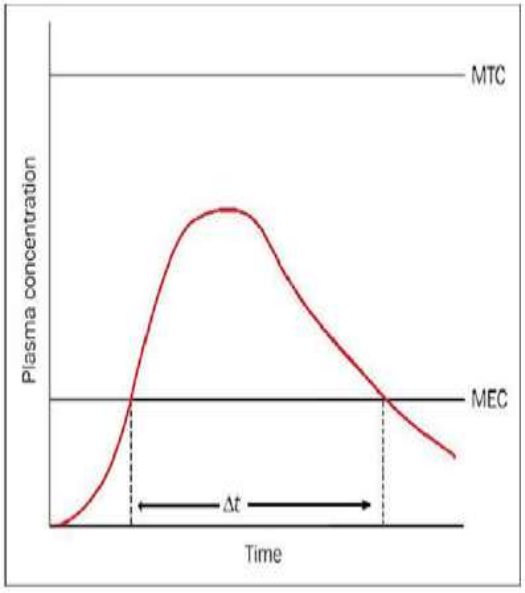

Fig : Plasma concentration vs Time

To calculate the dose of a drug for children based on Age:

1. YOUNG'S RULE :

AGE = less than 2 years

Young's Rule is an equation used to calculate pediatric medication dosage based on the age of the patient, as well as the known recommended adult dose. The definition of Young's Rule is the age of the patient, divided by the age added to twelve, all multiplied by the recommended adult dose.

Child dose = (Adult dose) × (Age/ Age+12)

2. COWLING'S RULE :

AGE = greater than 2 years

In order to solve problems based on dosage of drugs, we need to know what Cowling's rule is. It is the method that is used to determine the dosage of a drug to be prescribed for a child based on his age.

Child dose = Adult dose × **[**Age at next birthday / 24]

3. FRIED'S RULE FOR INFANTS :

AGE = for infants less than 1 year

Fried's Rule is another method used to calculate the correct dose of medication for the pediatric patient when given only the adult dose. This method should not be considered as accurate as the nomogram method because it is based on the assumption that the child is of average size and utilizes age rather than weight. It is important to note that because age does not necessarily indicate the patient's weight, medication adjustments may be necessary once the patient's response is determined.

Child dose = Adult dose × (Age in months / 150)

To calculate the dose of a drug for children based on body weight :

1. CLARK'S RULE

Clark's Rule is a medical term referring to a procedure used to calculate the amount of medicine to give to a child aged 2-17. The procedure is to take the child's weight in pounds, divide by 150lbs, and multiply the fractional result by the adult dose to find the equivalent child dosage.

Child dose = Adult dose ×[weight in(lb) /150 (average weight of adult in lb)]

To calculate the dose of a drug for children based on body surface area as related to weight :

1. Many physicians believe that doses for children should be based upon body surface area, since the correct dosage of drugs seems more proportional to the surface area..

Approximate dose for child = Adult dose x (BSA of child (in m2))

1.73 m2 (average adult BSA)

If dose for m2 is given

Approximate dose for child =

Dose per m2 **X** BSA of child (in m2)

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- **PATHOLOGICAL STATES:**

The effects of certain drugs may be modified by the pathological condition of the patient and must be considered in determining the dose. Warning and precautions are used in the drug labeling to alert the physician to certain restrictions in the use of a particular drug.

- **PHARMACEUTICAL DOSAGE FORM AND DRUG PHYSICAL STATE:**

Increasing the surface area of a drug by the reduction of its particle size has a significant effect on the rate of absorption, therefore, the dose can be minimized by reducing the particle size. Thus, crystalline and amorphous forms of a drug shows a significant difference in the rate of absorption.

- **POSOLOGY IN VETERNARY DOSE :**

The dose required for animals are more or on higher in comparison of human beings just because of body weight, size etc. Therefore it's very important for supply the correct dose.

It is mentioned earlier that doses depend upon the type of formulation ,age of the patient ,Sex of the patient ,idiosyncrasy,drug interaction,body weight ,Surface area and the severity of the disorder .

Thus,as compared to human beings ,the dose required for animals are more or on the higher side ,obviously because the weight and surface area of animals is normally more than in the case of human beings,except very few small animals.

Doses for animal as are normally mentioned on body weights.Morever unless otherwise mentioned specifically doses are applicable to 'all- species'.

The term all species as referred in British Pharmacopoeia Veterinary 1977 First Edition is restricted to

Horse and cattle. 500Kg Pigs. 150Kg

Sheep's ,goats,calves and Foals. 50 Kg Dogs. 10Kg Cats.05Kg

For heavier animals,the daily doses may vary.The word daily means once in twenty four hours.

Doses mentioned are per Kg of body weight of animals..

II. CONCLUSION:

Further studies in different settings using different methods of teaching, planned continuing education for all qualified nurses, and appropriate pass marks for students in critical skills are recommended.

This article has provided an overview of how to calculate drug doses but it is important to practise these skills regularly to help avoid errors that can result in patient harm.

- Many medication errors are due to health professionals not understanding the units of measurement or making mistakes in their calculations
- A number of medication errors are caused by failure to convert between different units of measurement correctly
- The main weight measurements nurses must be familiar with, and confident converting between, are grams, milligrams, micrograms and nanograms.
- It is important to be able to explain calculation methods and how you arrived at an answer
- Double-checking is recommended for all complex calculations, with each nurse doing the calculation independently, then checking the answer together.

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