

Factors affecting Drug metabolism.

UNIT-1 Last Topic
①

- > The rate of drug metabolism is important for its pharmacological action of the drug.
- > The increase in the rate of drug metabolism will decrease the intensity, duration of action and efficacy of the drug.
- > But the decrease in the rate of drug metabolism may lead to the accumulation of drug to toxicity level.

The various factors that may effect drug metabolism are:-

- 1) Age
- 2) Sex
- 3) Species
- 4) Strain
- 5) Genetic or hereditary factor
- 6) pregnancy
- 7) enzyme induction
- 8) enzyme inhibition
- 9) stereo chemical aspects.
- 10) Miscellaneous factors.

① Age:-

- > Difference in drug metabolic rate in diff. age group is mainly due to variation in enzyme content, enzyme activity and thermodynamics.
- > In humans, oxidative & conjugative capabilities of newborn are low compared with those adults.
- > So in neonates many drugs are biotransformed slowly.
- eg:- ① Caffeine half life is 4 days in neonates in comparison to 4 hours in adult.
- ② Tolbutamide half life is 8 hrs in adults, but in infants it is more than 40 hrs.

② Sex:-

- > The rate of metabolism also varies acc. to gender.
- > A marked diff. is observed b/n female & male rats, the male rats have greater drug metabolizing capacity.
- > Rabbits & mice do not show a significant sex difference in drug metabolism.
- > In humans, there have been few reports on sex difference.
- eg: ① Nicotine & Aspirin are metabolized diff. in men & women.
- ② Benzodiazepines are metabolized slowly in women than men.
- ③ oral contraceptives metabolize number of drugs at a slow rate.

③ species:-

- > species diff has been observed in phase I & II reactions.

eg:- metabolism of amphetamine occurs by two main pathways. (2)
oxidative deamination / aromatic hydroxylation.

* In humans, rabbits + guinea pig oxidative deamination is predominant pathway.

* In rat - aromatic hydroxylation.

* In humans phenytoin undergoes aromatic oxidation.

(4) Strain:-

→ strain diff. in drug metabolism exist particularly in inbred mice & rabbit.

→ The differences are caused by genetic variation in the amount of metabolizing enzyme present among the diff. strain.

eg:- In vitro, cotton ~~tail~~ rabbit liver microsomes metabolizes 10 times faster than New Zealand rabbit liver microsomes.

(5) Hereditary or Genetic factor.

→ Many genetic factors are responsible for the large diff in the rate of metabolism of these drugs.

eg: Biotransformation of Isoniazid by acylation varies among different races.

(6) Pregnancy:-

→ studies in animals show that the maternal drug metabolizing ability is reduced during the later stage of pregnancy.

→ This is due to high steroid hormone level during pregnancy.

eg: In women, the metabolism of promazine & pethidine is reduced during pregnancy or when receiving oral contraceptives.

⑦ Enzyme Induction:-

→ The activity of drug metabolizing enzyme can be increased by certain drugs, pesticides, polycyclic aromatic hydrocarbon. This process is termed as enzyme induction.

→ Inducers may increase the rate of their own metabolism as well as those of other unrelated drugs.

eg:- Induction of microsomal enzyme by phenobarbitone ↓es the metabolism of warfarin, which ↓es the ~~can~~ anticonvulsant activity when administered together.

⑧ Enzyme Inhibition:-

→ Inhibitors are agents, which ↓es rate of metabolism.

→ enzyme inhibition generally results in prolonged action of drug.

eg:- Inhibitors Drugs which ↓es metabolism.

phenylbutazone

(S)- Warfarin.

Allopurinol

6-mercaptopurine.

Isoniazid

phenytoin.

⑨ Stereochemical Aspects :-

③

- Many drugs are administered as racemic mixture.
- The two enantiomers present in the racemate may metabolize in diff. rates.

eg:- less active (+) - propranolol metabolizes more rapidly than the (-) enantiomer.

S(-) warfarin is 5 times more active than R(+)-Warfarin because latter metabolizes rapidly.

⑩ Miscellaneous factors :-

- i) dietary factors like protein to carbohydrate ratio
- ii) physiological factors such as pathological state of liver hormonal disturbances & circadian rhythm.