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BCH ASSIGNMENT

1 Discuss in Details the factors affecting drug metabolism

A number of factors may influence the metabolic rate of drugs, some of them are;

1 Chemical factors
a Enzyme Induction
b Enzyme Inhibition
c Environmental Chemicals
2 Biological factors
a Age
b Diet
c Sex Difference
d Genetics
e Species Difference
f Strain Difference

3 Physicochemical properties of the drug

4 Altered physiological factors
a Pregnancy
b Hormonal imbalance
c Disease states

5 Temporal factors
a Circadian rhythm
b Circannual rhythm
6 Drug administration route

1 Chemical factors

a Enzyme Induction

The phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals is called enzyme induction and agents which bring about such effect are called enzyme inducers. Some examples include Ethchlorvynol, enhances metabolites of warfarin, Phenytoin enhances metabolism of cortisol and digitoxin, Rifampicin increase metabolism of digitoxin. others are; barbiturates, chloral hydrate

Drugs which are significantly affected by enzyme induction:
Phenytoin, Warfarin, Tolbutamide, Imipramine, Oral contraceptives.

When drugs are given over a prolonged period of time, upregulation of enzymes takes place. Most of the time cytochrome P450 is involved leading to increased synthesis of new enzymes. The rate of metabolism increases as enzyme induction takes place.

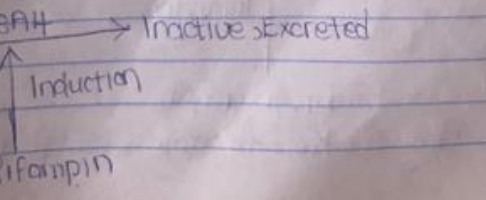
Mechanism of enzyme induction
- Increase in both liver size and liver blood flow.
- Increase in both total and microsomal protein content.
- Increased stability of enzymes.
- Increased stability of cytochrome P-450
- Decreased degradation of cytochrome P-450.
- Proliferation of smooth endoplasmic reticulum.

Consequences of Microsomal Enzyme induction
1. Decreased intensity and duration of action of drugs eg failure of contraceptives.
2. Increased intensity of action of drugs activated by metabolism Eg acute paracetamol toxicity is due to one of its metabolites.
3. If drug induces its own metabolism eg carbamazepine it develops tolerance so effects are not produced.
4. Precipitation of acute intermittent porphyria: Enzyme induction might increase porphyrin synthesis.
5. Intermittent use of an inducer might interfere adjustment of dose of another drug eg oral anticoagulants, oral hypoglycemics, antiepileptics and antihypertensives.

Categories of Inducers

I Auto Induction - The phenomenon in which a drug induces metabolism of other drugs as well as its own Eg carbamazepine, antiepileptic: (II) Phenobarbital type & Polycyclic hydrocarbon type.

An Example of drug induction



b) Enzyme Inhibition

The process by which drug metabolizing capacity of cytochrome is decreased is known as enzyme inhibition. The rate of metabolism is decreased. Drugs bringing about these changes are known as enzyme inhibitors. Examples include ketoconazole - antifungal drug, cimetidine and verapamil - calcium channel blocker.

Enzyme inhibition is a rapidly occurring process, most critical for drugs having a large therapeutic index. Competition for the active sites takes place between the enzymes and the drugs. When an enzyme inhibitor attaches, less metabolism occurs. The rate of metabolism is decreased, plasma levels of parent drug are increased while that of metabolites are less. Serious drug to drug interactions might occur, as the plasma half life is also increased.

The process of inhibition may be direct or indirect.

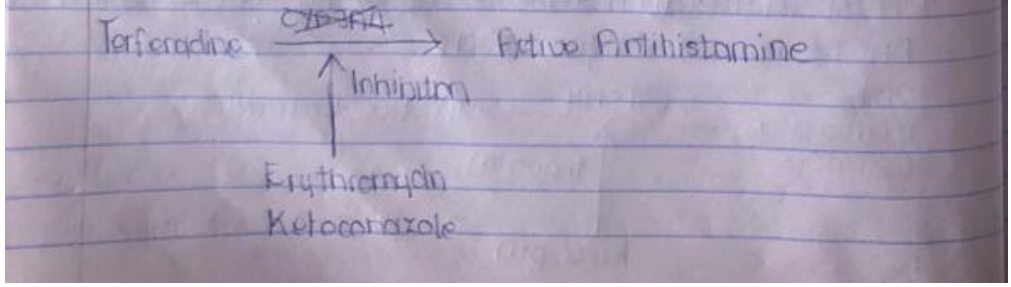
I Direct inhibition: It may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:

- Competitive inhibition: occur when structurally similar compounds compete for the same site on an enzyme.
- Non-competitive inhibition: occurs when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs
- Product inhibition: occurs when the metabolic product competes with the substrate for the same enzyme

II Indirect Inhibition: It is caused by the following mechanism

- Repression: It may be due to fall in rate of enzyme synthesis or rise in the rate of enzyme degradation.
- Altered physiology: It may be due to nutritional deficiency or hormonal imbalance

Example of enzyme inhibition



c Environmental Chemicals

Several environmental agents influence the drug metabolizing ability of enzymes. For example:

- Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.
- Organophosphate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drug metabolising ability of enzymes.
- Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere etc.

2 Biological factors

a Age

The drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and thermodynamics.

- In neonates (up to 2 months) and infants (2 months to 1 year), the microsomal enzyme system is not fully developed. So many drugs are metabolized slowly. For eg caffeine has a half life of 4 days in neonates in comparison to 4 hrs in adults.
- Children (between 1 yr and 12 yrs) metabolize drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 yrs. As a result they require large mg/kg dose in comparision to adults.
- In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of decreased cardiac output, all of which contributes to decreased metabolism of drugs. For example chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose.

b Diet

The enzyme content activity is altered by a number of dietary components. Generally;

- low protein diet decreases and high protein diet increases

The drug metabolizing ability or enzyme synthesis is promoted by protein diet and also raises the level of amino acids for conjugation with drugs.

- Fat free diet depresses activity some P-450 levels phospholipids, which are important components of microsomes become deficient.
- Grapefruit inhibits metabolism of many drugs and improve their bioavailability.
- Dietary deficiency of vitamins like A, B_2, B_3, C & E and minerals such as Fe, Co, Mg, Zn retard the metabolic activity of enzymes.
- Starvation results in decreased amounts of glucuronides formed than under normal conditions.

C Sex Difference

Gender related differences in the rate of metabolism are attributed to sex hormones and are generally observed following puberty.

Male have higher BMR as compared to the females, thus can metabolize drugs more efficiently eg salicylates and others might include ethanol, propranolol, benzodiazepines.

Women on oral contraceptives metabolize drugs at a slower rate.

d Species Difference

Drugs behave differently in different individuals due to genetic variation.

- Succinyl choline, which is a skeletal muscle relaxant, is metabolized by pseudocholine esterase. Some people lack this enzyme, due to which lack of metabolism of succinyl choline might occur. When administered in those individuals, prolonged apnea might result.
- Different groups of populations might be classified as fast metabolizers and poor metabolizers of drug.

For drugs like isoniazid, fast acetylators as well as slow acetylators are present. Fast acetylators cause rapid acetylation, while poor metabolizers, metabolize less. Hepatic acetyl transferase catalyzes acetylation. Slow acetylation might occur due to genetic malformation leading to decreased production.

e Species Difference

This has been observed in both Phase I & II reactions.

In those I reactions both qualitative and quantitative variations in the enzyme and their activity has been observed. Qualitative differences among species generally result from the presence or absence of specific enzymes in those species. Quantitative differences result from amount and localization of enzymes, the amount of natural inhibitors and the competition of enzymes for specific substrates. Human liver contains less cytochrome P-450 per gram of tissue than do the livers of other species. For example human liver contains 10 to 20 nmol/g whereas rat liver contains approximately 30 to 50 nmol/g of cytochrome P-450.

f Strain difference

This may be studied under two headings;

- Pharmacogenetics: A study of inter-subject variability in drug response. The inter-subject variations in metabolism may either be monogenetically or polygenetically controlled. A polygenetic control is observed in twins. In identical twins (monozygotic) very little or no difference in metabolism of halothane, phenylbutazone, dicoumarol and antipyrine was detected but large variations were observed in fraternal twins
- Ethnic variations: Differences observed in the metabolism of drug among different races. Such variations may be polymorphic or monomorphic - Eg; Approximately equal percent of slow and rapid acetylators are found among blacks and whites whereas the slow acetylators dominate Japanese and Eskimo population.

4 Altered Physiological factors

a Pregnancy

During pregnancy → metabolism of some drugs is increased while that of others is decreased due to the presence of steroid hormones eg phenytoin is increase, phenobarbitone is decreased and pethidine is decreased.

b Hormonal Imbalance

Higher levels of hormone may inhibit the activity of

of a few enzymes while inducing that of others eg
Hypothyroidism increases drug metabolizing capacity (increased half life of antipyrine, digoxin, methimazole, practolol) while hyperthyroidism decreases it.

c) Disease States
- Liver disease such as hepatic cardinal as cirrhosis, hepatitis, obstructive jaundice etc reduce the hepatic drug metabolizing ability and thus increases the half lives of almost all drugs.
- In renal diseases conjugation of salycylates, oxidation of vitamin D and hydrolysis of Procaine are impaired.
- Cardiovascular diseases, although have no direct effect, decrease the blood flow, which may slow down biotransformation of drugs like isoniazid, morphine and propranolol.
- Pulmonary conditions may decrease biotransformation. Procaine and procainamide hydrolysis is impaired.

3) Physicochemical properties of the drug
- Molecular size and shape
- pKa
- Acidity/basicity
- Lipophilicity
- Steric and electronic characteristics

5) Temporal Factor
Diurnal variations and variations in enzyme activity with light cycle is circadian rhythm.
Enzyme action is maximum during early morning and minimum in late afternoon which is probably due to high levels of corticosteroids.

6) Drug administration route:
- Orally administered drugs are absorbed from the GIT and are transported to the liver before entering the systemic circulation. Thus the drug is subjected to hepatic metabolism (1st pass effect) before reaching site of action.
- Sublingually and rectally administered drugs take longer time to be metabolized than orally taken drugs. Nitroglycerine

is ineffective when taken orally due to hepatic metabolism.
- IV administration would avoid first pass effect because the drug is delivered directly to the blood stream.