

INDUCTION AND INHIBITION OF DRUG METABOLISM

Induction and Inhibition

- Metabolism based drug-drug and other interactions can have a significant influence on the use and safety of many drugs.
- Induction of drug metabolism can lead to unexpected drops in drug concentration or the build-up of metabolites. The reverse can occur when there is inhibition of drug metabolism.
- The major organ involved in metabolism is liver and the major enzyme system involved in drug metabolism is CYP 450, the well-known family of oxidative hemo-proteins. Induction CYP 450 enzymes at the liver is responsible for induction of metabolism of many drugs.

Induction

- The phenomenon of increased drug metabolizing ability of the enzymes by several drugs and chemicals is called as enzyme induction.
- A number of drugs can cause an increase in liver enzyme activity over time. This in turn can increase the metabolic rate of the same or other drugs. Phenobarbitone will induce the metabolism of itself, phenytoin, warfarin, etc.
- Carbamazepine is another drug which can induce its own metabolism. Rifampin has been shown to cause up to a twenty times increase in midazolam metabolism. Cigarette smoking can cause increased elimination of theophylline (two fold increase) and other compounds. Dosing rates may need to be increased to maintain effective plasma concentrations.

Mechanism of enzyme induction and example for each mechanism:

Phenobarbitone induced accelerated metabolism:

- Oral anticoagulants, tricyclic antidepressants, corticosteroids, Theophylline, muscle relaxant zoxazolamine- Therapeutic efficacy of these drugs is reduced.
- Narcotic Drugs - Increase CNS depression with meperidine, increased active metabolites of meperidine.
- Pretreatment of phenobarbitone has also shown to markedly increase the metabolism of felodipine and its pyridine analogue.
- It can be observed from the examples that phenobarbitone induces the metabolism of many drugs, thus affecting the intensity and duration of the pharmacological action.

- Molecular mechanism: It leads to substantial increase in intra-nuclear RNAs that represent precursors to P450 and mRNA. The consequence of such increase is the substantial increase in the hepatic levels of certain P450 forms particularly CYP2B1 and CYP2B2, therefore, phenobarbitone is considered as a major inducible cytochrome P450.
- It can be concluded that the major inductive effect of phenobarbitone in the liver is to increase specific mRNA levels by augmenting transcription.

Hormone induced CYP 450 expression:

- Hormones induce induction of certain drugs like tamoxifen, tacrine, acetaminophen and xenobiotics like dietary phytochemicals and carcinogens like aromatic amines produced in cooking and those found in cigarette smoke.

Molecular mechanism: In the case of CYP1 family, this type of induction is mediated by specific aryl hydrocarbon (Ah) receptor.

The best known example is induction of CYP 450 enzymes of polycyclic aromatic hydrocarbons, which combine with specific receptor (in a similar manner to hormone response), resulting an inducer-receptor complex.

- This complex is trans-located to the nucleus of the hepatocytes where induction-specific mRNA is transcribed from the DNA. In the nucleus, the trans-located Ah receptor forms a heterodimer (with a second nucleic protein), which will bind to a common response element known as xenobiotic responsive element, that functions as a transcriptional enhancer, resulting in stimulation of gene transcription.
- Large amounts of newly translated, specific CYP 450 are then incorporated into the membrane of hepatic endoplasmic resulting in induction of drugs and xenobiotics.

Induction by inhibition interaction:

- Isoniazid, ethanol and some xenobiotics induced CYP 2E1 and CYP3A1.

Molecular mechanism: This is inhibitor mediated interaction with the heme group of the cytochrome P450s, resulting in inhibition of endogenous function and consequent disruption of endogenous pathways catalyzed by specific cytochrome P450 forms.

Well known example is induction of CYP2E1 by isoniazid and CYP3A1 by macrolide antibiotics. Apart from drugs, some xenobiotics also induce CYP2E1, this induction happens through multiple mechanisms at various levels from transcription to mRNA stabilization which increases in translational efficiency, and post-translational protein stabilization.

Another well-known case is the ethanol which at low concentration results in stabilization and inhibition of degradation of CYP2E1 apo-protein.

Most Enzyme Inducers have following properties:

- They are lipophilic compounds.
- They are substrate for the induced enzyme system.
- They have long elimination half lives.

Mechanisms involved in enzyme induction are:

- Increase in both liver size and liver blood flow.
- Increase in both total and microsomal protein content.
- Increase in stability of enzymes.
- Increase in synthesis of cytochrome P-450.
- Proliferation of smooth endoplasmic reticulum.

Consequences of enzyme induction includes:

- Decrease in pharmacological activity of drugs.
- Increase in activity where the metabolites are active.
- Altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones.

INDUCERS**DRUGS WITH ENHANCED METABOLISM****BARBITURATES**

Coumarins, Phenytoin, Cortisol, Testosterone, Oral Pills

ALCOHOL

Phenobarbital, Coumarins, Phenytoin

PHENYTOIN

Cortisol, Coumarins, Oral Pills , Tolbutamide

RIFAMPICIN

Coumarins, Oral Pills , Tolbutamide, Rifampicin

CIGARETTE SMOKE

Nicotine, Amino azo-dyes

Inhibition

- The phenomenon of decreased drug metabolizing ability of the enzymes by several drugs and chemicals is called as enzyme inhibition.

The process of inhibition may be of two types:

- [1]. Direct Inhibition
- [2]. Indirect Inhibition

Direct Inhibition;- It may result from the interaction of enzyme site, the outcome being a change in enzyme activity. Direct inhibition can occur by one of the three mechanisms:

- **Competitive inhibition:** This occurs when 'normal' substrate and the inhibitor substrate share the structural similarities. Many enzymes have multiple drug substrates that can compete with each other.
- Eg: Methacholine inhibits metabolism of Ach by competing with it for cholinesterase.

- **Non-competitive inhibition:** It arises when structurally un-related agent interacts with the enzyme and prevents the metabolism of drugs. Since the interaction is not structurally specific, metals like Lead, Mercury, Arsenic and Organophosphorous insecticide inhibits the enzymes non-competitively.
- Eg: Isoniazid inhibits the metabolism of Phenytoin by the same enzymes.
- **Product Inhibition:** This occurs when metabolic product generated by the enzyme inhibits the reaction on the substrate (feedback inhibition). This usually occurs when the product has physical characteristics very similar to that of substrate.
- Eg: Xanthine Oxidase inhibitors (Allopurinol) and MAO inhibitors (Phenelzine) also inhibits the enzyme activity directly.

Indirect Inhibition;- It is brought about by one of the two mechanisms:

- **Repression:** is defined as the decrease in enzyme content. It may be due to fall in the rate of enzyme synthesis as affected by ethionine, puromycin and actinomycin-D or because of rise in the rate of enzyme degradation such as by Carbon tetrachloride, Carbon disulphide, Disulphiram etc.
- **Altered Physiology:** due to nutritional deficiency or hormonal imbalance.

Enzyme inhibition is more important clinically than enzyme induction, especially for drugs with narrow therapeutic index, Eg: anticoagulants, antiepileptics, hypoglycemics, since it results in prolonged pharmacological action with increased possibility of precipitation of toxic effects.

INHIBITORS

DRUGS WITH DECREASED METABOLISM

MAO
inhibitors

Barbiturates, Tyramine

Coumarins

Phenytoin

Allopurinol

6-Mercaptopurine

PAS

Phenytoin, Hexobarbital

Inhibition of Biliary Excretion

Drug interactions in biliary excretion:

- Drugs are often conjugated and excreted in bile. Some drugs are excreted in bile biotransformation.
Eg: In humans most water soluble drugs and metabolites of relatively high molecular weight (more than 450) are excreted largely in the bile.
- This excretion is mainly via transporters and possibility exists for drug interaction with concomitant administration.
- Conjugates such as glucuronides are often excreted in bile and deconjugated in the intestinal tract and reabsorbed enterohepatic circulation.
- Drug interaction in the process of biliary excretion may affect the residence time and AUC of unchanged drug plasma.

○ Hepatobiliary Drug Interaction:

| Transporter | Drug | Inhibitor | Result of interaction |
|-------------|---------|------------|--|
| P-gp | Digoxin | Quinidine | Decreased in biliary excretion |
| MR1*2 | SN-38 | Probenecid | Decreased in biliary excretion Results in increased AUC |

- The co-administration of drugs which inhibits the co-transporter involved in biliary excretion can reduce the biliary excretion of drug which are substrates of the transporter, leading to elevated plasma drug concentration.

Eg: Biliary and urinary of digoxin, both mediated by p-gp are inhibited by Quinidine which is an inhibitor of p-gp.

Effect on biliary excretion:

- Verapamil and cyclosporine are both inhibitors of p-gp, but through different mechanism, verapamil is a substrate for p-gp and is a competitive inhibitor of this pump, where as cyclosporine inhibit transport function by interfering with substrate recognition and ATP hydrolysis.
- Decrease clearance of drug through inhibition of p-gp translates clinically in to increased AUC and increased in toxicity.
- Examples:
 - * Decreased in vincristine clearance in presence of verapamil.
 - * Decreased in paclitaxel or etoposide clearance in presence of chromophore.
 - * Decrease in itoposide or doxorubicin clearance in presence of cyclosporine

Application of induction and inhibitions

- Understanding inhibition and induction of drug metabolism and its inhibition potential helps in new drug development.
- Metabolism based drug-drug and other interactions can have a significant influence on the use and safety of many drugs
- Role of receptors can be studied by understanding the molecular mechanism of induction of drug-metabolizing enzymes.
- Induction-mediated drug-drug interactions can be evaluated in p450 protein induction in-vivo PK studies
- The scenario of drug-drug interaction can be derived from P-gp inhibition or induction
- The different responses of a receptor to the action of a drug can be studied at where the enzymatic inhibition takes place

Reference:

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THANKYOU...