Clinical Implications of Enzyme Induction and Enzyme Inhibition

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Summary

The pharmacological effect of a drug is partly dependent upon its concentration at its site of action, which in turn is partly dependent upon its rate of elimination. The rate of elimination of many lipophilic drugs is governed by the activity of the hepatic microsomal mixed-function oxidases. Consequently any alteration in the activity of these enzymes may result in a modification of drug action.

A wide range of chemically unrelated substances may stimulate the activity of the mixed-function oxidases by enzyme induction. The drugs most frequently encountered as enzyme-inducing agents in man are barbiturates, rifampicin and phenytoin. Enhancement of drug metabolism by ethanol, tobacco smoking and diet may also involve enzyme induction. Enzyme induction is normally associated with a reduction in drug efficacy but may also alter the toxicity of certain substances.

Enzyme induction has been assessed in man by measuring changes in the pharmacokinetics of a marker drug, or changes in the disposition of endogenous compounds such as γ-glutamyltranspeptidase, D-glucaric acid and 6β-hydroxycortisol.

The therapeutic problems associated with enzyme inhibition have received much less attention than those associated with enzyme induction. The effect on the rate of elimination of a particular drug will depend upon the fraction of the dose that is normally metabolised by the inhibited enzyme and on the affinity of the enzyme for the drug and the inhibitor. An alteration in the dosage schedule is usually only necessary for drugs with a small therapeutic ratio.

The pharmacological effect of a drug is partly dependent upon its concentration at its site of action, which in turn is determined by several factors such as absorption, distribution and elimination. The rate of elimination of many drugs is governed largely by the rate of metabolism, and therefore any change in the activity of the drug-metabolising enzymes may result in a modification of drug action.

The major site of drug metabolism is the liver, although it is becoming increasingly obvious that other tissues such as white blood cells, placenta, skin, lung and especially the gut may play an important role in the metabolism of drugs. The essential physiological action of the drug-metabolising enzymes is to convert lipophilic drugs into more water-soluble metabolites which are more readily excreted. Drug metabolism consists of phase I reactions such as oxidation, reduction and hydrolysis, and phase II reactions which include conjugation with glucuronic acid, sulphuric acid, mercapturic acid and amino
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Acids (Williams, 1974). Quantitatively, the most important enzymes are the hepatic microsomal P-450 mixed-function oxygenases which, by simply 'inserting' oxygen into drug molecules, are able to effect numerous biotransformations, including aliphatic and aromatic hydroxylation, N-, S-, and O-demethylation, deamination, dechlorination and desulphurisation.

A wide range of chemically and pharmacologically unrelated agents, including drugs, are able to alter the activity of the drug-metabolising enzymes. The action of these enzymes may be enhanced by enzyme induction which involves a selective increase in the concentration of a particular enzyme relative to the concentration of microsomal protein in the cell. Alternatively, the activity of these enzymes may be reduced by enzyme inhibition, which as the name suggests involves direct action on the enzyme rather than any change in enzyme synthesis.

The therapeutic implications of enzyme induction and enzyme inhibition will depend largely on the relative biological activity of the drug and its metabolite(s). In many cases the metabolites are therapeutically less active than the parent drug, and consequently the extent and duration of drug action will be potentiated by enzyme inhibition and reduced by enzyme induction. It is important to realise that the effects of enzyme inhibition and enzyme induction are reversible and that withdrawal of the interacting agent will also produce a change in the pharmacological action of the drug affected.

From a clinical point of view such drug interactions will be most obvious for drugs with a narrow therapeutic range, such as oral anticoagulants and antiarrhythmic agents. The action of these drugs should be carefully monitored, therefore, whenever other drugs are co-administered.

As well as producing quantitative changes in drug metabolism, enzyme induction and enzyme inhibition may also produce qualitative changes in the metabolism of a drug. Such changes may have toxicological implications, especially if there is an increased production of a chemically reactive metabolite, which theoretically may lead to unwanted side effects, including thrombosis, hypersensitivity, carcinogenesis, dysmorphogenicity and tissue necrosis.

1. Enzyme Induction

Drug-induced enhancement of microsomal enzyme activity in man is thought to be mediated by enzyme induction rather than allosteric changes (Conney, 1967). The phenomenon of enzyme induction involves an adaptive increase in the number of molecules of a specific enzyme (Gelehrter, 1976) in response to an enzyme-inducing agent. The hepatic drug-metabolising enzymes are probably unique in that they can be induced by such a wide range of biologically and chemically unrelated compounds, including drugs, steroids and environmental pollutants. The molecular mechanism of enzyme induction involves genomal derepression, but the initial step in the process is not known nor have the molecular characteristics essential for induction been defined. Inducers of drug oxidation have several features in common such as lipophilicity, the ability to bind to cytochrome P-450 enzymes and relatively long biological half-lives. However, many drugs share these properties without inducing enzyme synthesis.

On the basis of animal work, it was originally thought that inducing agents fell into 2 categories, one represented by phenobarbitone (phenobarbital) which induced P-450 enzymes and one represented by 3-methylcholanthrene which induced P-448 enzymes. More recent work has shown that this classification is an over-simplification both in terms of enzyme-inducing agents and the oxygenases whose activity they alter. Several groups of chemicals including barbiturates, aromatic hydrocarbons, steroids and biogenic amines are known to induce multiple forms of the enzymes concerned with drug oxidation. There is now direct evidence for multiple forms of P-450 in human hepatic microsomes (Kahn et al., 1980). The enzyme systems involved in phase II metabolism, such as glutathione transferase and glucuronyl transferase, can also be induced.

The time course of induction varies with the in-