Drug metabolism

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Drugs are eliminated from the body by various mechanisms. Elimination includes both excretion and metabolism and it is the latter that will be reviewed in this article.

Classical pathways of drug metabolism

The aim of drug metabolism is to change drugs from an active to an inactive molecule, this often involves changing them from lipid- to water-soluble compounds. Drugs that are lipid-soluble are able to cross biological membranes; water-soluble drugs find it more difficult but can be excreted in the bile and urine. It should be remembered that, to the body, drugs are but one of many foreign substances (xenobiotics) requiring metabolism everyday.

Drug metabolism usually involves enzymes. The greatest mass of enzymes is found in the liver, hence the importance of liver disease on drug metabolism. However, many drug metabolising enzymes are found in other sites. Indeed, the greatest concentrations of some of these enzymes are found in organs such as the nose and adrenal gland. Some enzymes are predominantly extra-hepatic and metabolism of drugs by these enzymes is often independent of liver disease.

The classical pathway of drug metabolism involves two phases. Phase I usually involves the transfer of molecular oxygen and maybe an oxidation, reduction or hydroxylation reaction. This produces an intermediate metabolite. These intermediate metabolites may be highly reactive and toxic. For example, the intermediate metabolite of paracetamol, *N*-acetyl–*p*-benzoquinone (NAPQI), is toxic to the liver and kidneys. Usually, the phase I product is conjugated with glucuronic acid or sulphate or a similar group to produce the final inactive metabolite. For example, NAPQI is conjugated with glutathione to render it inactive. When an overdose of paracetamol is taken, glutathione stores are exhausted and the phase I metabolite accumulates, resulting in toxicity.

The common enzymes responsible for phase I metabolism are the cytochromes P 450 (CYP) although others, including alcohol dehydrogenase, aldehyde dehydrogenase, alkylhydrazine oxidase, amine oxidases, aromatases and xanthine oxidase can also perform this type of metabolism. CYPs are found mostly in the endoplasmic reticulum. They are a super-family of about 20 enzymes in humans that used to be identified by their substrate specificity. Now they are identified by their amino-acid homology. An enzyme family has a 40% similarity and is identified by Roman numerals. The sub-family has 55% similarity and is identified by a capital letter, while the gene product is identified by a further numeral. Thus, nifedipine oxidase and cyclosporin oxidase are now identified as CYP 3A4. This particular CYP is an important enzyme because it metabolises almost 60% of commonly-used drugs (Table 1).

Phase II enzymes are mostly cytoplasmic and present in much larger amounts than phase I enzymes. Some drugs, *e.g.* morphine and lorazepam, are not metabolised initially by phase I enzymes; they are only metabolised through phase II reactions to glucuronides.

There is increasing interest in extra-hepatic enzymes in anaesthesia, especially the esterases. These are found in many tissues as well as the blood and there are many different types. Butyryl cholinesterase (pseudocholinesterase) is well known because of its importance in the metabolism of succinylcholine. However, the new opioid remifentanil is also metabolised by many non-specific esterases, rather than a single enzyme. This results in a 'built-in redundancy' with respect to its enzymatic degradation.

Key points

In an individual patient, the ability to metabolise drugs may change over a short time.

Many drugs used in the operating theatre and intensive care unit are inhibitors or inducers of enzyme function.

Drugs given intravenously are often dissolved in solvents which may accumulate resulting in toxicity.

Intermediate metabolites of drugs may be toxic.

Genetic differences in some enzymes may result in a variations in activity.

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Intracellular expression of enzymes

The amount (expression) of an enzyme in the cell is determined by many different factors. Some of these are described below.

Genotype

Enzymes are proteins and their expression in the cell is determined by the genotype. For example, several genetically different forms of CYP 2D6 have been recognised for some time. This enzyme metabolises the anti-hypertensive drug debrisoquine (amongst others, see Table 1). During its development, one of the investigators noted that, after self-administration, the hypotensive effect of debrisoquine lasted longer than in other subjects. He measured his urinary metabolites of debrisoquine and found they were low and realised this might be due to a genetic variation in the enzymes responsible for its metabolism. It is now recognised that there are more than 13 different variants. Genetic abnormalities also occur in phase II enzymes. For example, in Gilbert's syndrome, bilirubin cannot be conjugated and jaundice develops because of unconjugated hyperbilirubinaemia. Similarly, genetic abnormalities of butyryl cholinesterase have been well characterised, with four variants of this enzyme being described (*i.e.* normal, atypical, fluoride resistant, silent).

Sex

In some animals, there are differences in the expression of enzymes between the sexes (sexual polymorphism). This is not seen in humans, but enzyme activity can be influenced by hormonal factors, *e.g.* CYP 3A4 is affected by sex-related differences in the patterns of growth hormone excretion.

Age

There are substantial differences in the expression of enzymes at the extremes of age. Morphine is metabolised primarily to morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G). The appearance of these metabolites has been used to assess the development of enzyme systems in premature infants and children. The M-3-G:morphine ratio in plasma and urine and the M-6-G:morphine ratio in urine were lower in the premature infants than in children. This suggests that glucuronidation pathways increase with age. Since there was no difference in the M-3-G:M-6-G ratio, it is likely that the two metabolic pathways develop together.

The ability to metabolise drugs decreases with advancing years. Even with drugs that have many different enzymes available for metabolism (*e.g.* remifentanil), elimination reduces with age.

Hypoxaemia

Liver blood flow is reduced in many situations, including sepsis, mechanical ventilation, non-traumatic stress and surgery. Reduction in liver blood flow decreases oxygen delivery to the hepatocytes. This is worsened by the reduced ability of the cell to extract oxygen from the blood in many of these conditions. Thus, hepatic hypoxia is common in many ill patients. Reductions in the expression of CYP 3A in hypoxic human hepatocytes have been reported. In the sick patient, there is also a decrease in drug delivery, which will have most effect on drugs with a high hepatic extraction ratio.

Table 1 The major enzyme (or sub-family) metabolising some of the commoner drugs used in anaesthesia and intensive care (note the importance of the 3A subfamily). Other enzymes, not shown here, may also be involved (especially CYP 2E1).

	CYP 1A	CYP 2C	CYP 2D6	CYP 3A		CYP 1A	CYP 2C	CYP 2D6	CYP 3A		CYP 1A	CYP 2C	CYP 2D6	CYP 3A
Mefenamic acid		+			Digoxin				+	Pancuronium		+		
Valproic acid		+			Erythromycin				+	Paracetamol	+			+
Alfentanil				+	Fentanyl				+	Pethidine				+
Amitriptyline			+	+	Fluconazole				+	Phenacetin	+			
Bupivacaine	+			+	Glibenclamide		+		+	Phenformin			+	
Carbamazepine				+	Haloperidol			+	+	Phenobarbitone		+		
Chloramphenicol		+			Imipramine	+	+	+	+	Phenylbutazone		+		+
Chlorpromazine			+	+	Itraconazole				+	Phenytoin		+		+
Chlorpropamide		+		+	Ketoconazole				+	Prednisolone				+
Cyclosporine				+	Lidocaine				+	Propranolol	+	+	+	
Cimetidine	+			+	Methoxyflurane				+	Theophylline	+			+
Codeine			+	+	Metoprolol		+	+		Thiopental		+		
Cortisol				+	Methylprednisolone				+	Thioridazine			+	+
Cyclophosphamide		+		+	Metronidazole				+	Tolbutamide		+		+
Dantrolene				+	Midazolam				+	Tramadol			+	+
Debrisoquine			+		Nifedipine				+	Verapamil	+	+		+
Dexamethasone				+	Nimodipine				+	Warfarin	+	+		+
Diazepam		+		+	Omeprazole		+		+					
Diclofenac		+			Ondansetron	+		+	+					

Inflammatory mediators

In sepsis and other inflammatory conditions, mediators are released that have wide-ranging effects. Some of these (*e.g.* IL-1, IL-4, IL-6, TNF-α, IFN-γ) decrease the expression of enzymes.

Nutrition

Prolonged starvation and diets deficient in vitamins A, C and E decrease cellular concentrations of CYPs. High protein, lipid or low carbohydrate diets lead to an increase in some enzymes resulting in enhanced metabolism of some drugs, *e.g.* theophylline. In the obese, conjugation and oxidation reactions are increased while acetylation reactions are unchanged.

Endocrine factors

Endocrine abnormalities are surprisingly common. Patients may acquire them before the presenting illness, or they may develop during illness or as a result of treatment. Insulin decreases the half-life of messenger RNA for some CYPs in isolated hepatocytes. Hyperthyroidism increases the activity of CYPs and corticosteroids have also been shown to induce some of them.

Temperature

Abnormalities of temperature are common also. An increase in temperature usually increases the rate of a chemical reaction. However, in a patient, this is sometimes offset by the cause of the fever. Antipyrine is a test substrate for cytochromes P 450. When volunteers were given a pyrogen, the rate of antipyrine metabolism was reduced. Similarly, in patients with malaria-induced fever, antipyrine metabolism was also reduced. Conversely, when patients were given esmolol during cardiopulmonary bypass, the rate of metabolism was predictably reduced. The difference between these observations can be explained by the mechanism of the change in temperature. Inducing a fever with a pyrogen or hyperpyrexia as a consequence of disease will induce the release of inflammatory mediators that appear to have an effect greater than that of the fever. Reducing temperature during cardiopulmonary bypass does not induce the same inflammatory response.

Enzyme inhibition and induction

This is a common problem in critically ill patients who are given many drugs. Inhibition may lead to accumulation and toxicity of drugs while induction may reduce plasma and effector site concentrations leading to a decrease in effect. A good example is the treatment of methicillin-resistant *Staphylococcus aureus* infection. Microbiologists may suggest initial treatment with rifampicin which is a very potent inducer of CYP 3A4. Later, quinupristin/dalfopristin (Synercid®) may be substituted and this is a potent inhibitor of this enzyme.

Many drugs affect the enzyme that metabolises them. For example, the phase I metabolite of the antidepressant nortriptyline inhibits the enzyme that metabolises it. Substrate inhibition may occur when erythromycin is given with midazolam resulting in prolonged coma. Inhibition of CYP 3A4 may also occur with propofol. The mechanism is thought to be a direct action of propofol on the haem part of the enzyme that donates oxygen to the chemical reaction. There is some debate whether this has clinical significance. Foodstuffs may also act as enzyme inhibitors. Grapefruit juice inhibits no fewer than 9 cytochrome P 450 enzymes. Not all enzyme inhibition is detrimental. For example, dehydropeptidase 1, found in the brush border of renal tubules, breaks down the carbapenem antibiotic, imipenem, reducing its effectiveness in renal tract infections. The co-administration an enzyme inhibitor (cilastatin) enhances the efficacy of the antibiotic.

Induction of enzymes is associated with many drugs – rifampicin, barbiturates and corticosteroids are amongst the commonest. Unlike inhibition, which can occur immediately after a single dose, induction of enzymes takes approximately 24–48 h to occur. Certain drugs (*e.g.* sulphinpyrazone) can inhibit the metabolism of some drugs (*e.g.* theophylline) but induce the metabolism of others (*e.g.* phenytoin, warfarin).

Pathway switching

Many drugs may be metabolised by a variety of pathways resulting in different metabolites. For example, paracetamol may be metabolised both to a glucuronide and a sulphate conjugate. When rats were infected with malaria and given a low dose of paracetamol, total clearance of the drug was the same as in those who were not infected. However, there was a decrease in glucuronide and an increase in sulphate production. When a higher dose was used, there was a decrease in total clearance and glucuronide formation. Other influences on pathway switching include oxygenation but the mechanism of this is unclear.

Changes in enzyme function

Enzyme function and ability to metabolise drugs may reflect the overall condition of the patient and change as this improves or deteriorates. Usually as the patient's condition improves, so the ability to metabolise drugs also increases. Conversely, if the patient's condition worsens, so metabolism is often decreased. Thus, pharmacokinetic variables derived from healthy volunteers or patients may not apply to the critically ill. Furthermore, pharmacokinetic variables measured on one particular day may not apply later in the disease.

Protein binding

In the blood, drugs exist as free drug (active and available for metabolism) and that bound to proteins (inactive and unavailable for metabolism). Drugs may bind to several proteins in the blood including lipoproteins and elements of the erythrocyte. However, albumin and α_1-acidoglycoprotein bind most drugs.

If the drug is highly protein-bound and some is displaced from its binding site, there will be an increase in its action. However, if the capacity exists to metabolise it, there will be a brief increase in action before the equilibrium between free- and bound-drug is restored.

Serum concentrations of albumin decrease with stress although, in the beginning of illness, this may be a redistribution phenomenon rather than a reduction in total body albumin. It has two binding sites which carry mostly acidic drugs, such as phenytoin and lidocaine. These binding sites appear to be affected by pH and other factors and they are competed for by several different drugs. Conversely, α_1-acidoglycoprotein increases after stress, *e.g.* surgery, carcinoma. It binds mainly basic drugs such as morphine. Some drugs (*e.g.* prednisolone) may bind to more than one protein.

Metabolites

One of the purposes of drug metabolism is the ability to convert active drugs into inactive metabolites. However, there is increasing recognition that some metabolites are active. For example, M-6-G is active at the opioid receptor and M-3-G may be anti-analgesic and induce seizures. Pharmacological activity is surprising as these metabolites are water-soluble. However, a group from Switzerland explained this by considering the shape of the metabolite molecule. There is a single bond in one part of the molecule that allows its configuration to change. It is lipid-soluble in a lipid environment and water-soluble in an aqueous environment. They christened these molecules 'molecular chameleons'. Other drugs that have active metabolites include midazolam (1-hydroxy-midazolam and 1-hydroxy-midazolam glucuronide), diazepam (nor-desmethyl-diazepam, oxazepam), vecuronium (nor-desacetyl vecuronium) and meperidine (nor-meperidine). Even the new opioid, remifentanil, has an active metabolite, although this only has 1/4000th the activity of the parent compound.

Solvents and metabolism

In many injectable formulations, lipid-soluble drugs are dissolved in solvents as they will not form aqueous solutions of sufficient concentration. Solvents are either organic (*e.g.* propylene glycol) or fat emulsions (*e.g.* soya bean extract) and also undergo metabolism before excretion. The normal metabolic pathways for solvents are often deranged in a similar way to those of drugs. Since large amounts of solvent may be given, accumulation can occur. Propylene glycol is used to dissolve many drugs including lorazepam, diazepam, cotrimoxazole and etomidate. Toxicity, including renal failure, lactic acidosis and seizures has been reported with this solvent.

Propofol is solubilised in a fat emulsion and toxicity can occur when excessive amounts are given. Patients may develop lactic acidosis and myocardial failure which may be fatal. We have recently had experience of a patient who appears to have had a genetic abnormality of an enzyme that is responsible for the transport of fat within the cell.

Key references

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See multiple choice questions 117–121.