

Prodrugs

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The term prodrug is usually applied to compounds that are inactive in their parent form(s) but which, after administration, are chemically transformed to the active derivative. The concept was proposed some 30 years ago (Albert, 1958) although drugs that fulfil these requirements have been in clinical use since the turn of the century. Some authors use the term more loosely to encompass compounds that are active in parent form but also have active metabolites which are responsible for much of the clinical effect, e.g. benzodiazepines and tricyclic antidepressants. Such drugs are not considered in this article. The important features of prodrugs are illustrated schematically in Figure 1.

Prodrugs may be kept in their inactivated form either by a covalent linking or by ionic bonds, such as salts of the active moiety. The most common prodrug linkage is an ester bond (Figure 2), while phosphate salts form the majority of the rest. Activation of most prodrugs

is by an enzymatic process that cleaves off the active moiety. This may be achieved by hydrolytic digestive enzymes once the compound has left the stomach. However, carboxylesterases such as those found in the liver, duodenum, kidney and brain hydrolyse ester bonds more efficiently than enzymes in the gut lumen. Prodrugs are occasionally designed to be activated by non-enzymatic chemical degradation but this is generally less predictable due to problems inherent in formulating a chemically unstable molecule. For a few drugs, transformation occurs in a biosynthetic pathway when the substance is an analogue of a naturally occurring enzyme substrate.

It is important that the inactive moiety should be non-toxic and preferably rapidly eliminated from the body. For most indications it is also desirable that the activation process should be rapid once the prodrug has reached the site of action.

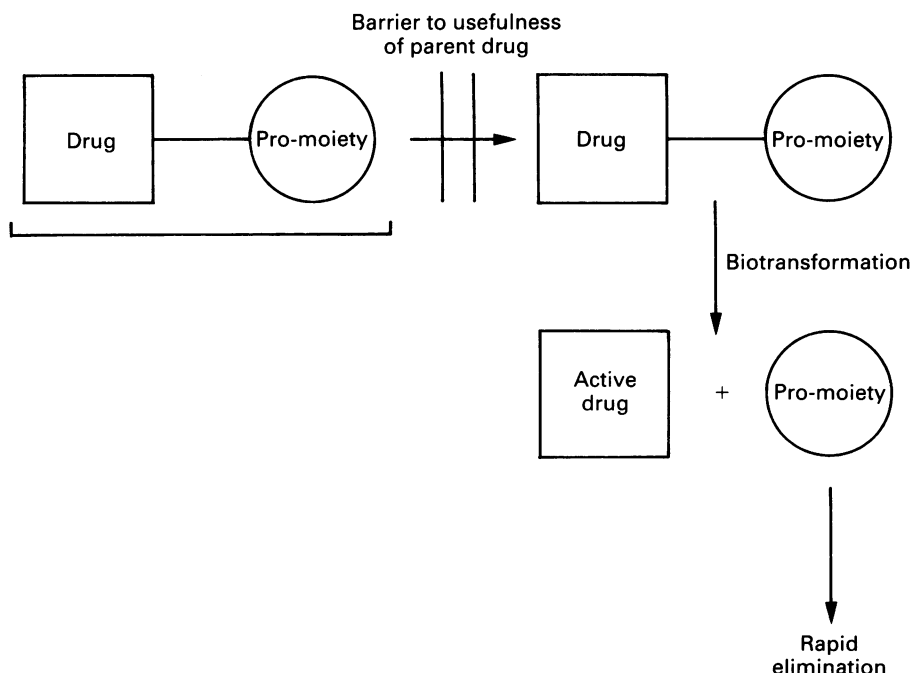


Figure 1 Schematic representation of the concept of prodrugs.

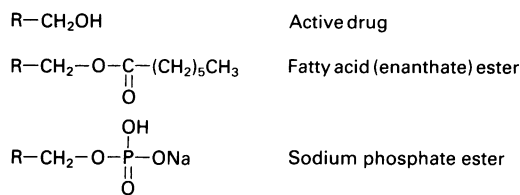


Figure 2 Examples of ester bond linkages in prodrug formulation.

Rationale for prodrug formulations

Many prodrugs in clinical practice started life as modifications of existing drugs to overcome an inherent disadvantage of the active molecule. Increasingly, however, new compounds are being designed in prodrug form. There are two major rationales for prodrug formulations.

Pharmaceutical problems

Some useful active compounds have been formulated as prodrugs to surmount such problems as unpalatability, gastrointestinal irritation or pain on injection. Other prodrugs achieve greater solubility or stability than the active compound.

Pharmacokinetic problems

Several pharmacokinetic reasons exist for developing prodrugs:

- To achieve more complete or predictable absorption of the drug.
- To reduce incomplete and variable systemic bioavailability by preventing extensive pre-systemic metabolism.
- To improve access to the site of action, e.g. penetration of the blood-brain barrier.
- To activate selectively a drug in the intended target tissue, thus avoiding undesirable systemic effects.
- To optimise either the rate of onset or duration of action of a drug by improving absorption, distribution or elimination characteristics.

This review considers several prodrugs in clinical use and examines the success and limitations of this approach to drug formulation.

Examples of clinically useful prodrugs

Gastrointestinal system

Sulphasalazine Treatment of colonic inflammation with minimal systemic unwanted effects requires local delivery of the therapeutic agent.

Sulphasalazine is an example of a polar molecule that is partly absorbed orally, then excreted in the bile. It is metabolised in the colon by anaerobic bacteria, releasing 5-aminosalicylic acid and sulphapyridine. High tissue concentrations are achieved in the colonic mucosa and access gained to a greater part of the colon than can be achieved by rectal administration. However, 5-aminosalicylic acid is the active agent and most unwanted effects of sulphasalazine relate to systemic absorption of sulphapyridine. Therefore, 5-aminosalicylic acid may be preferable to the prodrug in this situation. Sulphasalazine has recently also been used to treat rheumatoid disease when sulphapyridine is probably an important anti-inflammatory component perhaps by reducing antigen absorption from the gut.

Stimulant laxatives Prodrugs are often used as laxatives and help to achieve a degree of colonic targeting. For example, Bisacodyl (diphenol diacetate) is hydrolysed in the small bowel to diphenol, which is absorbed and undergoes glucuronide conjugation in the liver. The conjugate is excreted in the bile and transformed in the colon to active diphenol. A similar fate befalls other phenolphthalein derivatives.

Senna is an anthraquinone derivative given as a glycoside prodrug. Bacterial hydrolysis in the colon release the active aglycones sennosides A and B.

Cardiovascular system

Enalapril Enalaprilat is a potent inhibitor of the angiotensin converting enzyme and is an effective treatment for hypertension and heart failure. In this active form, less than 12% is absorbed from the gut. The inactive monoethyl ester derivative enalapril has an improved absorption of between 50% and 75% (Swanson *et al.*, 1984; Ulm *et al.*, 1982) and conversion to enalaprilat occurs by de-esterification in the liver (Howlett, 1983). Peak enalapril concentrations occur in blood 1 h after oral dosing, while peak enalaprilat concentrations are found at about 3 to 4 h. Relatively slow excretion of enalaprilat by glomerular filtration further prolongs the duration of action and permits once daily dosing for most patients. A potential disadvantage of prodrugs is that the extent of activation may be unreliable, especially in the presence of liver disease. Although there are no data to suggest a disadvantage in clinical practice, the advent of long-acting inhibitors of angiotensin converting enzyme that are active in parent form, e.g. lisinopril, may make prodrugs less attractive. Several new prodrug angiotensin converting enzyme inhibitors are currently

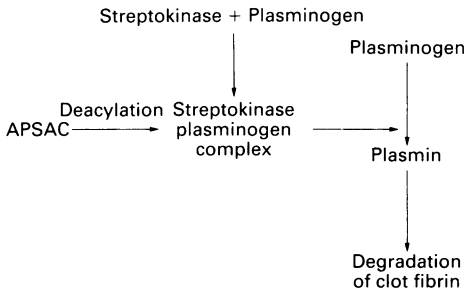


Figure 3 An outline of the fibrinolytic system and its activation by streptokinase or APSAC.

undergoing clinical trial e.g. ramipril (Patchett *et al.*, 1980), cilazapril (Attwood *et al.*, 1984) and perindopril (Lees *et al.*, 1985).

α -Methyldopa Orally administered amines do not cross the blood-brain barrier but neutral amino acids such as α -methyldopa are transported into the brain by a specific carrier system. The affinity of this transport system for amino acids greatly exceeds that of other tissues (Pardridge, 1983), creating a degree of target specificity. α -Methyldopa is subsequently concentrated in neuronal cells where it becomes a substrate in the catecholamine biosynthetic pathway and is transformed into α -methylnoradrenaline. The latter is a weak neurotransmitter and stimulates presynaptic α -adrenoceptors to reduce central sympathetic outflow and lower blood pressure.

Dopamine analogues Dopamine, by stimulating β -adrenoceptors, augments myocardial contractility and low doses act at specific dopamine receptors to dilate renal arteries. It is widely used to manage oliguria in low cardiac output states, but poor oral bioavailability restricts its use to short-term intravenous infusion.

The orally active prodrug L- γ -glutamyl-dopamine utilises the high renal content of the enzyme γ -glutamyl transpeptidase to deliver dopamine selectively to the kidney (Kyncl *et al.*, 1979). L- γ -glutamyl-L-dopa (Wilk *et al.*, 1978) uses the same enzyme to release L-dopa from which renal aromatic amino acid decarboxylase produces dopamine.

An alternative approach is ibopamine, the inactive N-methyldopamine 3,4-diisobutyryl ester which is under evaluation for treatment of chronic heart failure. After oral absorption it is hydrolysed to epinine which has similar properties to dopamine (Randolph *et al.*, 1983).

Sulphinpyrazone Originally introduced as a uricosuric, sulphinpyrazone also inhibits platelet

aggregation. The sulphide metabolite produced by reduction of sulphinpyrazone and the oxidation product, the sulphone metabolite, probably account for the majority of this clinical effect (Buchanan *et al.*, 1978; Pay *et al.*, 1980). Sulphinpyrazone may therefore be considered a prodrug for its antiplatelet effects. After oral administration of sulphinpyrazone, the delay of some hours before the sulphide metabolite is found in blood is consistent with its production by colonic bacteria (Renwick *et al.*, 1982; Strong *et al.*, 1984).

Thrombolytic agents Streptokinase, the most widely used thrombolytic agent for acute myocardial infarction, achieves its effect by generation of a circulating streptokinase-plasminogen complex which catalyses activation of free plasminogen to plasmin (Figure 3). However the subsequent clot dissolution is also accompanied by significant systemic fibrinolysis and the consequent risk of haemorrhage.

Anistreplase (anisoylated plasminogen streptokinase activator complex, APSAC), is a proenzyme complex acylated at the plasminogen active site (Smith *et al.*, 1981). The inactive complex has a higher affinity for fibrin, particularly if present in clot, compared with fibrinogen. Slow deacylation of the complex while bound to the clot (Ferres *et al.*, 1987) gives the complex a 'fibrinolytic half-life' of about 120 min compared with 20 min for streptokinase *in vitro* (Fears *et al.*, 1987). Thus, while streptokinase requires prolonged infusion, a bolus injection of anistreplase is sufficient for clot lysis. However, despite greater clot specificity and inactivation of circulating anistreplase by α_2 -antiplasmin, it is uncertain whether haemorrhagic complications are less frequent than with streptokinase (Cairns *et al.*, 1989).

Tetranicotinoylfructose Nicotinic acid is a poorly tolerated vasodilator due to rapid absorption and high plasma concentrations leading to transitory effectiveness accompanied by flushing and fainting. Tetranicotinoylfructose is an ester of nicotinic acid which is slowly hydrolysed by the alkaline content of the small intestine. The gradual release of nicotinic acid makes the compound more acceptable for therapeutic use.

Respiratory system

Theophylline derivatives Although oral absorption of theophylline is rapid, it has low water solubility and formulation is difficult. Formation of salts with choline or ethylenediamine improves solubility, and dissociation at gastric pH releases

the active drug. The ethylenediamine salt (aminophylline) also shows one of the disadvantages of prodrug formulation since after intravenous injection the ethylenediamine has been reported to cause hypersensitivity reactions (Howarth & George, 1983).

Theophylline salts have a short duration of action and prodrugs with low solubility can prolong the duration of action by slow dissolution with subsequent rapid hydrolysis after absorption. Of these, the most promising was 7,7'-succinyl-ditheophylline but it is unclear whether this approach offers any advantages over slow release formulations of theophylline salts.

Central nervous system

Antipsychotic depot injections Adequate plasma concentrations of many antipsychotic drugs are important for therapeutic efficacy. Poor compliance of schizophrenic patients with long-term oral treatment can be overcome with intramuscular depot injections. The most common formulations are inactive fatty acid esters, usually the enanthate or decanoate derivatives. To delay attack by tissue aliphatic esterases, the injection is given in an oily solution. Injection of active drug in oily solution results in far higher initial concentrations and a less prolonged duration (Dreyfuss *et al.*, 1976). Compounds available in depot prodrug formulations include fluphenazine, flupenthixol and clopenthixol.

L-dopa Dopamine is not absorbed orally or transported across the blood-brain barrier. L-dopa is a polar prodrug of dopamine which is transported by the neutral amino acid carrier system both across the gut wall and into the brain (c.f. methyl-dopa). The most important metabolic route is via aromatic amino acid decarboxylase (AAAD), an enzyme widely found in the gut mucosa, liver and kidney. Therefore, considerable metabolism will occur before the prodrug reaches the brain. Peripheral conversion to dopamine has been utilized experimentally in the treatment of heart failure but the major application for the drug is in Parkinson's disease. To achieve adequate brain concentrations and avoid systemic effects of dopamine (e.g. nausea, hypotension) requires selective inhibition of peripheral decarboxylation with an AAAD inhibitor that does not cross the blood-brain barrier.

Chloral hydrate Chloral hydrate cannot be formulated as a solid and prodrug complexes have been used to circumvent this problem. The compound dichloralphenazone was widely used

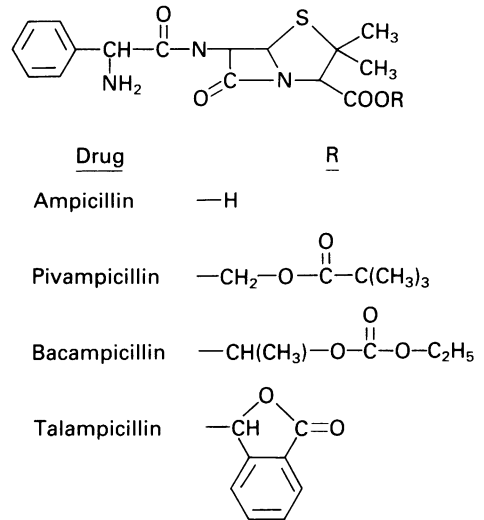


Figure 4 Ampicillin and its three prodrug esters.

as a hypnotic until recently, but adverse reactions to pyrazolone derivatives, to which phenazone is related, have led to its substitution by chloral betaine. The trimethyl glycine moiety, which dissociates from the chloral hydrate in the stomach, is considered to be a safer alternative.

Diamorphine Morphine crosses the blood-brain barrier relatively slowly. Diacetylmorphine (heroin) has greater lipid solubility and thus transfer into the brain, where hydrolysis converts diamorphine to morphine. The latter is responsible for the clinical effects (Inturrisi *et al.*, 1984) and a more rapid onset of opiate action is achieved.

Infections

Penicillin derivatives Ampicillin, an acid resistant semi-synthetic penicillin, is a highly polar molecule with a variable and low oral bioavailability. Large oral doses are required to achieve adequate tissue concentrations, therefore considerable amounts reach the colon and modify colonic flora which leads to a high incidence of diarrhoea.

Addition of an ester group to the carboxyl terminal of ampicillin inactivates the drug and makes it more lipophilic, thus improving oral absorption. The majority of ester hydrolysis occurs rapidly after absorption so that drug remaining in the gut is mainly inactive and less likely to cause diarrhoea (Leight *et al.*, 1976). Three esters of ampicillin are currently available (Figure 4). Pivampicillin (pivaloyloxymethyl ester) releases formaldehyde and pivalic acid;

subsequent metabolism of the small amount of formaldehyde prevents toxicity. Talampicillin (pthalidylthiazolidine ester) releases 2-carboxybenzaldehyde and bacampicillin (ethoxycarbonyloxyethyl ester) releases acetaldehyde, carbon dioxide and ethanol. Plasma concentrations of ampicillin attained with these esters are up to five times higher than those seen after oral ampicillin (Leight *et al.*, 1976; Ehrnebo *et al.*, 1979; Rozenzweig *et al.*, 1976). Pivampicillin may have advantages over the other esters since it undergoes least hydrolysis in the intestine before absorption.

Mecillinam is an amido penicillin with a broad spectrum of gram negative antibacterial activity. Oral absorption is extremely low, but the pivmecillinam ester prodrug increases the urinary recovery of mecillinam from 5% to 45%. Similarly, carbenicillin, useful for pseudomonas infections, is restricted to parenteral use. The prodrug carbenicillin indanyl ester (carfecillin) has improved acid stability and oral absorption but blood concentrations of carbenicillin after oral carfecillin are still low, and therapeutic concentrations are achieved only in the urine (Wilkinson *et al.*, 1975).

Chloramphenicol Although serious bone marrow toxicity restricts the use of this drug, it is still useful for severe infections such as those caused by *Salmonellae*. The bitter taste of liquid oral formulations was overcome by using the inactive chloramphenicol palmitate. Low water solubility makes the ester tasteless, but hydrolysis in the gut by pancreatic lipase ensures adequate absorption of active drug.

Improved characteristics of chloramphenicol for parenteral use were achieved by the different approach of creating a highly water soluble ester with sodium succinate. However, slow hydrolysis of the ester bond results in excretion of appreciable amounts of prodrug via the kidney (Nahata & Powell, 1981).

Clindamycin Clindamycin also has an unpleasant bitter taste; inactive and tasteless esters such as the palmitate are used to formulate the syrup. Hydrolysis in the gut or gastrointestinal mucosa ensures that almost all of the circulating drug is in active form. For parenteral use, the phosphate-ester avoids pain on intramuscular injection and local irritation occurring after intravenous use of the base drug. Hydrolytic activation after infusion may be slow but there is little excretion of prodrug.

Erythromycin Acid lability makes erythromycin base unsuitable for oral use. Enteric coating leads to variable and unpredictable bioavailability and, therefore, acid stable inactive esters are used for oral administration. The stearate ester hydrolyses in the small intestine to release the active drug, while erythromycin estolate (the laurylsulphate salt of the propionyl ester) is absorbed unchanged and slowly hydrolysed by tissue esterases. Higher total blood concentrations are achieved with the estolate, although active drug concentration may be higher after the stearate (Welling *et al.*, 1979). Thus, the slower rate of ester hydrolysis with the estolate is less desirable.

Metronidazole Occasionally used as a suspension, metronidazole is another example of a drug with an unacceptably bitter taste. In this case it is overcome by use of the ester benzoylmetronidazole.

Hexamine One of the earliest prodrugs to be used clinically, hexamine chemically degrades to release formaldehyde if the environmental pH falls below 5. Enteric coating protects hexamine in the stomach and it is eliminated unchanged in the urine. Release of the potentially toxic metabolite is thus limited to acid urine where it exerts antibacterial activity. Initially used to dissolve renal stones, the observation that it relieved symptoms of urinary tract infection was fortuitous.

Acyclovir This analogue of guanosine is selectively activated by the herpes virus, which produces two unique enzymes that are not found in human tissues. The viral deoxynucleoside kinase initially converts acyclovir to a monophosphate form (Elon *et al.*, 1977; Fyfe *et al.*, 1978). Subsequent enzymatic action generates the active triphosphate derivative, which then inhibits herpes virus DNA polymerase (Elon, 1982). The specific activity of acyclovir in herpes-infected cells provides an excellent example of selective cell targeting using a prodrug design.

Endocrine system

Glucocorticoids Improved water solubility of several glucocorticoids, e.g. methylprednisolone, hydrocortisone, was necessary for parenteral formulations. Instability of the sodium succinate prodrug formulation necessitates reconstitution of a lyophilised powder at the time of injection, and a further disadvantage is incomplete hydrolysis. However the alternative disodium phosphate ester may cause unpleasant perineal irritation.

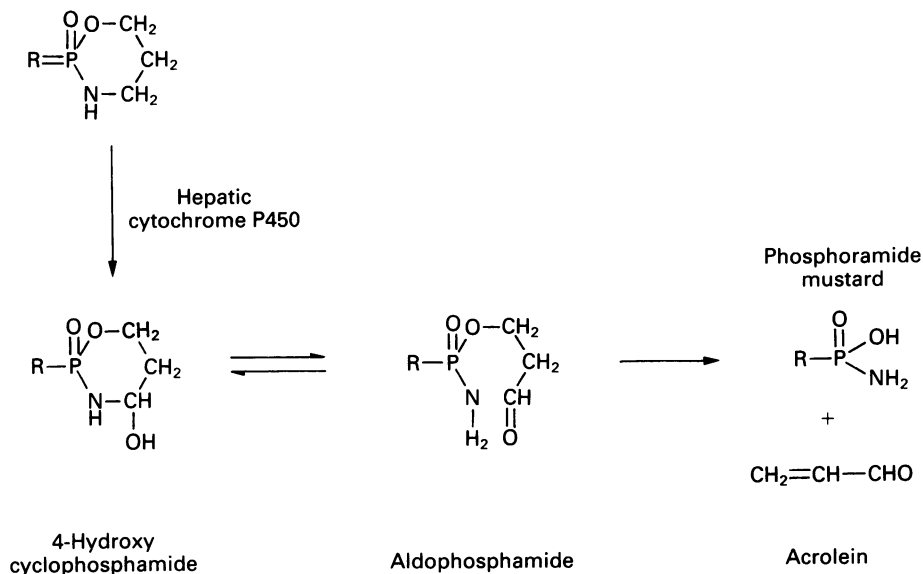


Figure 5 The activation pathway of cyclophosphamide.

Sex hormones Several prodrugs of testosterone are available for replacement therapy by intramuscular depot injection, using a formulation similar to that for anti-psychotic drugs. Of these, the propionate, undecanoate and enanthate esters are most widely used. Slow release of the ester from the oily vehicle followed by initial redistribution of the lipophilic compounds to adipose tissue, permits intervals of up to 4 weeks between injections. Similar preparations of oestrogen are also available for treatment of primary amenorrhoea, e.g. oestradiol benzoate.

When stilboestrol is used to treat prostatic neoplasia, systemic feminising effects are undesirable. The prodrug stilboestrol diphosphate was an attempt to exploit the high concentration of acid phosphatase in the prostate and achieve selective activation in the target organ. However, sufficient enzyme is present in other tissues to limit the specificity of this approach.

Malignant disease

Alkylating agents Most alkylating agents are administered in active form but cyclophosphamide is a prodrug that is activated in the liver. Initial conversion is to 4-hydroxycyclophosphamide, which is in spontaneous equilibrium with its acyclic tautomeric form, aldophosphamide; these function as inactive 'transport' molecules (Colvin *et al.*, 1976).

Subsequent spontaneous elimination of acrolein from aldophosphamide generates the active moiety phosphoramidate mustard (Figure 5). Despite activation in the liver, severe hepatotoxicity is unusual due perhaps to inactivation by aldehyde dehydrogenase of any aldophosphamide that is not released into the blood. Activation after absorption may reduce gastrointestinal toxicity but the major dose-limiting toxic effect of cyclophosphamide, haemorrhagic cystitis, is probably due to acrolein and, as a prodrug, cyclophosphamide can only be considered partially successful.

Dacarbazine is a less commonly used alkylating agent which is metabolised in the liver by *N*-demethylation. Non-enzymatic degradation of the metabolite releases diazomethane, the precursor of the cytotoxic methylcarbonium ion, and is enhanced in an acid environment. It has been suggested that the lower pH in tumour cells may encourage selective release of the active moiety. Only tentative evidence from mice supports this concept.

Antimetabolites Several examples of prodrugs are found in the purine and pyrimidine analogues which substitute for natural nucleotides and inhibit formation of nucleic acids. Conversion of 6-mercaptopurine to 6-mercaptopurine-ribose-phosphate is accomplished by the enzyme hypoxanthine guanine phosphoribosyltransferase

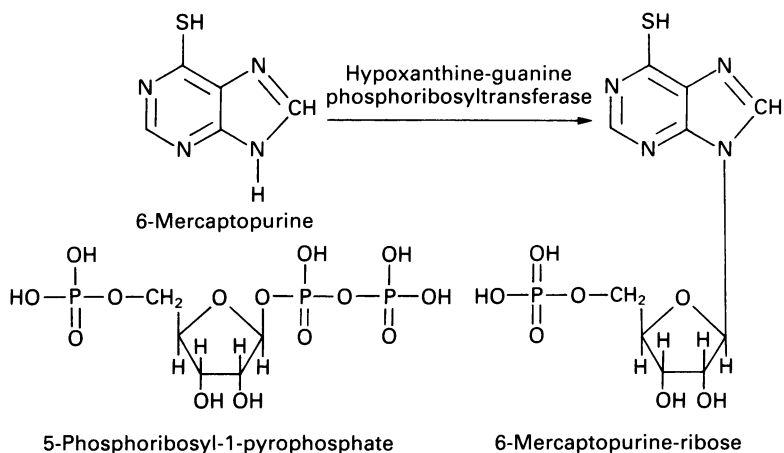


Figure 6 Biosynthesis of the active derivative of 6-mercaptopurine.

(Figure 6). The activated drug binds to and inhibits the regulatory site of an amidotransferase enzyme which is involved in the early stages of purine biosynthesis. Similar mechanisms are involved for 6-thioguanine and 5-fluorouracil.

Cytarabine, an antimetabolite, used in myeloid leukaemias, is activated to produce cytarabine triphosphate, a competitive inhibitor of DNA polymerase.

There is evidence that antimetabolite drugs have some selectivity for rapidly dividing cells and perhaps for malignant cell lines, but this may reflect the greater metabolic demand of such cells rather than selective activation.

Musculoskeletal and joint disease

Gastrointestinal irritation and ulceration are among the most common unwanted effects associated with non-steroidal anti-inflammatory compounds. The mechanisms are complex but intragastric release of active acidic drug is a contributory factor. Esterification of the carboxylic acid residue and consequent inactivation of the drug should reduce local gastric toxicity. However since systemic delivery of active drug to gastric mucosa also contributes to gastric damage (Clinch, 1986) prodrugs are unlikely to eliminate the risk.

Aspirin and benorylate Salicylates are among the most poorly tolerated of the non-steroidal anti-inflammatory drugs. Large doses of salicylic acid have both an unpleasant taste and cause a high incidence of gastrointestinal upset. Acetylsalicylic acid (aspirin) is more palatable and was an early example of the fortuitous use of a prodrug

in clinical medicine. Non-specific esterases which hydrolyse aspirin unfortunately have a high concentration in the gastric mucosal cells, releasing the irritant salicylic acid in the stomach.

An alternative approach is benorylate, which is an inactive ester of aspirin and paracetamol. It is absorbed intact, reducing local gastric irritation (Wright, 1975) and hydrolysed slowly after absorption. Unfortunately, the slow rate of acetylsalicylic acid release means that large doses are required (Rainsford & Whitehouse, 1980).

Fenbufen Fenbufen has no effect on the activity of prostaglandin synthetase *in vitro* but hepatic metabolism generates at least two active metabolites, biphenylacetic and γ -hydroxybiphenylbutanoic acid derivatives (Van Lear *et al.*, 1978).

Post-marketing surveillance suggested a low incidence of gastrointestinal irritation (Brock & Jackson, 1982), while microbleeding (Lussier *et al.*, 1983) and endoscopic mucosal appearance (Lanza *et al.*, 1983) during fenbufen treatment, also suggest a greater margin of gastrointestinal safety than with conventional non-steroidal anti-inflammatory drugs. However, all were short-term studies and the latter two used healthy volunteers who were younger than the population normally exposed to the drug.

Sulindac Sulindac is metabolised by two pathways to an inactive sulphone and by reversible reduction to the sulphide (Figure 7) (Duggan *et al.*, 1977, 1978). *In vitro* anti-inflammatory test systems considered relevant to *in vivo* efficacy (Duggan, 1981) and correlations between drug concentration and biological effect *ex vivo*

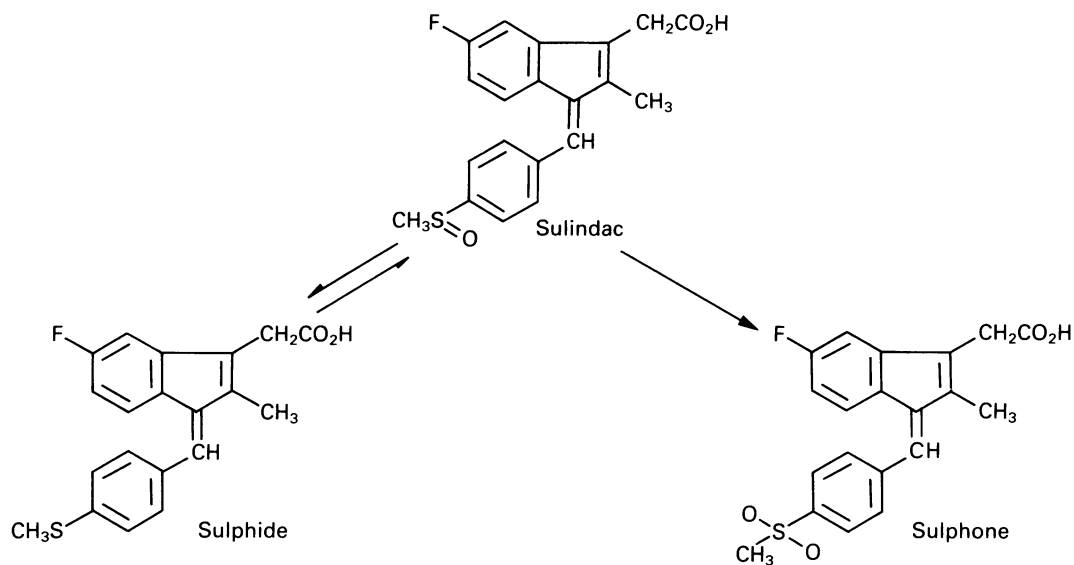


Figure 7 Metabolic activation and inactivation pathways of sulindac.

(Duggan *et al.*, 1977) suggest that sulindac is a prodrug. Re-oxidation of the sulphide to the parent form occurs before elimination, but the sulphide has a long half-life and prolonged duration of action. There is strong evidence that both the liver (Tatsumi *et al.*, 1983) and gut flora (Strong *et al.*, 1985) contribute to sulphide generation; secondary plasma peaks of the sulphide may reflect enterohepatic circulation of sulindac with sulphide formation in the colon. Whether the potential benefits of sulindac as a prodrug have been realised is uncertain. Evidence from open (Rhymer, 1979) and controlled trials (Gengos, 1978) does not allow adequate comparison with other ulcerogenic non-steroidal anti-inflammatory drugs.

Nabumetone Nabumetone is activated predominantly at first-pass through the liver; the major active metabolite is the oxidative product 6-methoxy-2-naphthylacetic acid (Morgan, 1985; Freeman *et al.*, 1985). Short-term studies of gastrointestinal blood loss and endoscopic studies, particularly in patients with arthritis and pre-existing gastrointestinal damage (Roth, 1987; Greb *et al.*, 1987), are encouraging that nabumetone may be less irritant than naproxen.

Eye

Dipivefrin The use of topical adrenaline to treat glaucoma is limited by poor corneal absorption and systemic unwanted effects. The ester

dipivaloyl-adrenaline penetrates the cornea more readily than the parent drug, and hydrolysis, during transfer releases adrenaline into the aqueous humour (Anderson, 1980). However, there is little difference between the systemic absorption of adrenaline or dipivefrin in animal studies (Anderson, 1980) and no clear evidence for a difference in clinical efficacy (Kriegelstein & Leydecker, 1978).

Will new prodrugs improve therapeutics?

This review has considered some of the prodrugs currently available. They demonstrate varying degrees of success in achieving the goals of prodrug design. Benefit has been realised by creating prodrugs that improve taste or gastric tolerance or irritation at injection sites. Modification of drug solubility or stability can improve absorption characteristics and systemic bio-availability or achieve an effective prolongation of drug action.

Selective drug targeting is conceptually one of the most exciting areas of prodrug application, but one which has seen relatively little success (Stella & Himmelstein, 1985). Improved uptake of drug into the target tissue is often insufficient to guarantee improved efficacy (Shashoua *et al.*, 1984), unless accompanied by selective activation by an enzyme present in high concentration in the target tissue. However, this will only be valuable if the activated drug does not rapidly

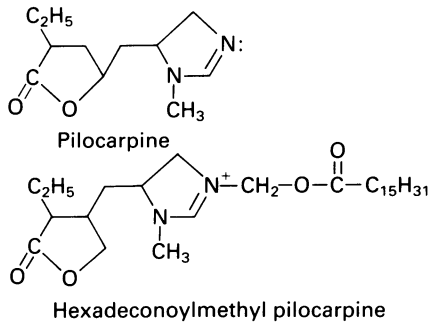


Figure 8 An example of a 'soft' quaternary amine.

diffuse away to equilibrate with other tissues. Monoamine oxidase inhibitor prodrugs can improve brain selectivity without inhibiting the enzyme in the gut wall. The obvious advantage is avoidance of the notorious 'cheese reaction' and, in animal models, the prodrug (E)- β -fluoromethylene-*m*-tyrosine has shown some success. Preferential decarboxylation by aromatic-amino-acid decarboxylase in monoamine nerves in the brain yields an enzyme-activated irreversible inhibitor of monoamine oxidase (Palfrey *et al.*, 1985). It seems unlikely that enzyme systems with sufficient specificity will be found to capitalize fully on the concept of site-specific delivery. Targeted prodrugs can be created by attaching the active moiety to a macromolecule, such as an antibody or glycopeptide which is bound to a specific cell-surface receptor. Phagocytosis of such a complex by reticulo-endothelial cells may restrict its use (Poste & Kirsch, 1983) but if it reaches the target site, uptake into the cell and lysosomal cleavage

will expose that cell line to the effects of the active drug.

New prodrugs may improve penetration across the blood-brain barrier. Examples include reduction in the polarity of quaternary amines such as pralidoxime and pilocarpine, by use of a prodrug moiety (Figure 8) (Bodor & Loftsson, 1987) an approach which also improves absorption from the gut. However, as for levodopa, peripheral activation may reduce its site specificity.

Conclusions

Prodrugs have partially fulfilled their promise in clinical practice. With some prodrugs clear advantages are apparent and justify substitution for the active agent. Good examples are the esters of ampicillin. For other compounds, such as enalapril, the prodrug was necessary to create a clinically useful formulation, but has no intrinsic merit and potential disadvantages. Theoretical benefits have not always shown convincing improvements in practice. Thus, some non-steroidal anti-inflammatory prodrugs should cause less gastro-intestinal irritation than similar active compounds, but clinical evidence to support this is scanty. The claimed advantages of prodrugs should always be critically assessed in the light of well conducted and relevant clinical trials.

Prodrugs clearly have a future and drug design will continue to utilize this approach to optimise the characteristics of new compounds. However, despite potential benefits, the concept carries limitations. For many compounds, alternative delivery systems may be more effective for achieving a desired goal.

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