REVIEW ARTICLE

Adverse reactions to drugs and their physico-chemical properties

J. G. LEWIS
M.D., F.R.C.P.

Edgware General Hospital, Middlesex HA8 0AD

Summary

Physico-chemical factors can be related to adverse reactions. Their importance is that safer drugs can be made at the stages of design, delivery and metabolism.

Introduction

There is now much information associating desirable and undesirable actions with chemical structure and constitution and physical properties. Hundreds of thousands of natural and synthesized compounds have been subjected to bacterial, animal and human toxicological studies and the information has been stored by computer and can be retrieved as an aid to literature search when embarking on new compounds. The reason for knowing which factors are harmful is that measures can be taken to avoid them and so design safer drugs. If the relationship between structure and toxic action is known then safer drugs can be made by molecular manipulation (Ariëns, 1980). Drugs may be inherently or primarily toxic, or may increase their toxicity or become so after biotransformation. Hence the metabolic study of a drug may also result in safer therapy. The following points will be discussed—molecular structure and constitution, toxophoric groups, molecular mimicry, chemical classes, pro-drugs, molecular weight, lipid-water solubility, ionization, protein binding and isomers.

Molecular structure and constitution

Some of the earliest structure-activity relationships were directed at aromatic polycyclic hydrocarbons. Some were potent carcinogens, others became so after biotransformation while others were inert. It was shown that the polycyclic hydrocarbon was usually a phenanthrene derivative with oncogenic epoxy and epoxydiol metabolites (Boyland, 1980). Empirical correlations were made: number of rings, molecular size, shape, thickness and substituents. The carcinogenic molecule was

flat or co-planar with, characteristically, areas free of substituents called bays. Strategically placed methyl groups could enhance or decrease carcinogenicity. Studies proceeded from identifying patterns, to metabolic transformation and then to the overall electron density in the molecules. Areas of special reactivity corresponding to regions of electron density were identified (e.g. K region) and the sites of epoxidation were related to electron distribution. Other carcinogenic molecules were found: aromatic amines, by virtue of N-hydroxylation and esterification; nitrosamines, by metabolism forming a reactive carbonium which alkylates natural cell polymers; nitrosamides; azo dyes; and alkylating agents (Connors, 1979; Selkirk, 1980). Unifying concepts were sought to explain how these agents, as well as ion-radicals and free-radicals, could cause cancer. The best answer is that carcinogens are all strongly electron-deficient and hence electrophilic. They will readily attack electron-rich nucleophiles such as the bases in DNA. Carcinogenic molecules are usually mutagenic and this has proved a useful screening test (Venitt, 1980). Electrophilic substances such as metronidazole are widely used and, while clinical experience with it is to date reassuring, careful follow-up of treated patients is advised (Goldman, 1980).

Toxophores

The importance of knowing which part of a structure is responsible for toxicity is illustrated by the time, research and money spent on the unpredictable and inexplicable behaviour of practolol. Certain groups are unduly associated with toxicity such as the thiourea moiety which causes marrow depression. Thus metiamide was replaced by cimetidine with the less dangerous cyanoguanidine group. Nitro groups gained a bad reputation in the form of nitrobenzene; chloramphenicol is an aliphatic derivative of nitrobenzene but the mechanism of causing marrow aplasia is unknown. Nitro-imidazoles are widely used but marrow depression is not one of their effects. Another

example of the value of identifying the toxophore is thalidomide. Studies showed it was the phthalimido group which reacted with DNA and accordingly chemists were able to modify its structure and produce the related taglutamide which does not appear to be teratogenic.

In other cases where metabolic studies have shown that toxic metabolites are formed the offending part of the molecule can be shielded sterically so as to prevent toxogenic metabolites. Another strategy is to introduce an alternative metabolic pathway, thus deviating metabolic conversion from a risky process to a safer attack on, for instance, an alkyl group (Ariëns, 1980; Ariëns and Simonis, 1979).

Antimetabolites

The introduction of sulphonamides led to the far-reaching concept of antimetabolites. Most in clinical use are analogues of purines, pyrimidines and folic acid. The structures may closely resemble the natural substance as with methotrexate, or be a stripped down, small molecule such as trimethoprim and pyrimethamine. Molecular mimicry, however finely designed, may lead to toxicity since selectivity for enzymes or receptors is never complete. For this reason trimethoprim and methotrexate by interference with DNA synthesis can cause megaloblastic anaemia. Nucleotide analogues are toxic from the accumulation of toxic precursors of nucleic acids. One way of avoiding this toxicity is to synthesize enzyme inhibitors which block pyrimidine formation early on in the biochemical pathway. N-(phosphonacetyl) L-aspartate or PALA is an attempt to do just this.

Chemical class

Knowing that a drug belongs to a family or class even though its medical application may differ can help to anticipate common adverse reactions. Hence, sulphinpyrazone and phenylbutazone which are both pyrazolidinediones interact unfavourably with warfarin. Sulphonamides, benzothiadiazines, β -lactam antibiotics, β -adrenoceptor blockers, opioids, tricyclic antidepressives and corticosteroids all can share adverse reactions of their family. The art of the chemist is to increase potency or selectivity while decreasing unwanted effects. Recognizable patterns of toxicity can occur within families; for instance, the side chain of phenothiazines markedly alters biological activity. Sedation is a feature of the shorter basic side chain of the antihistaminic phenothiazines whereas the longer side chain of the major tranquillizer is associated with different neurological syndromes according to whether an aliphatic, piperazine or piperidine moiety is present.

'Me too and me again' drugs

The lead drug has the run of the market so second and third generation drugs must possess something special to succeed. One clear advantage is safety during manufacture (Ariëns, 1980) as well as in the patient. Both the increase in potency and selectivity, by leading to smaller doses, possess advantages (Ariëns, 1980). Other advantages relate to pharmacokinetics.

Toxokinetic effects may be avoided by altering absorptive qualities, speed of onset, duration of action, metabolism and excretion. Toxic accumulation can be controlled by altering hydrophilicity or lipophilicity, or by ensuring rapid inactivation and elimination. Metabolically vulnerable groups on the molecule ensure a 'handle' which can be easily conjugated with glucuronic acid and lead to rapid excretion. Temazepam is a benzodiazepine which by virtue of a 3-hydroxy group on the nucleus achieves rapid elimination. Propanidid is an example of a drug containing a safe, labile and easily metabolized group so that it may act as a rapidly acting intravenous anaesthetic. At other times, a drug which produces active metabolites can be promoted as having advantages in that abrupt withdrawal symptoms are avoided—as with diazepam. On the other hand, other benzodiazepines have been deliberately made to have no active metabolites. Metabolically stable drugs have the advantage that dosage is more readily related to plasma levels.

Pro-drugs

Pro-drugs are designed according to strict physico-chemical constraints (Yalkowsky and Morozowich, 1980). Side effects such as diarrhoea due to high concentration of local drug can be minimized as illustrated by the various ampicillin esters. Ampicillin is amphoteric and by masking its carboxylic group is made more lipophilic with improved absorption. An important proviso is that the carrier should be non-toxic. Erythromycin estolate is a more lipophilic compound than erythromycin, but liver toxicity can arise from the estolate portion. Another use for pro-drugs is to mask unpleasant tastes as in the case of chloramphenicol palmitate. In chronic situations prolonged action with low concentration is an advantage; the latentiation of azathioprine is an example of another use for a pro-drug in minimizing side effects.

Molecular weight

Molecular weight (along with polarity) is one factor which determines whether a drug is excreted in the bile. Molecular weight of about 500 or more of the drug alone or the conjugate makes biliary

excretion likely, e.g. rifampicin and erythromycin. Conjugates (such as bile salts) are metabolized by mucosal enzymes or by bacteria into less polar forms and are then re-absorbed. Such entero-hepatic recycling is a mechanism whereby toxic or allergic reactions could be prolonged (Stenlake, 1979). The placental membrane is also relatively impermeable to large molecules.

Lipid-water solubility

The balance of water and lipid solubility can be altered predictably for many molecules. For instance, drugs entering the CNS are made very lipophilic and those confined to the gut, hydrophilic. Lipophilicity is associated with high protein binding, high hepatic extraction, high volume of distribution and an enhanced entry into the CNS and nerves. Biotransformation is required to render the drug water-soluble and polar. Lipophilic substances can be sequestered in adipose tissue especially if they are metabolically stable as is the case with DDT and certain plasticisers in disposable infusion sets. Active metabolites of lipophilic drugs if present in excessive amounts can overwhelm enzymatic degradation processes. Lipid soluble β -adrenoceptor blockers are associated with vivid dreams and nightmares.

Water-soluble hydrophilic drugs are excreted renally and, therefore, if there is renal impairment, toxic levels are likely. Aminoglycosides have this risk. They also have low protein binding, low volume of distribution and are poorly absorbed orally. Water soluble tetracyclines are also dangerous in renal failure, but not the lipophilic doxycycline.

Ionization

Most drugs are weak acids or bases and exist as a mixture of ionized and un-ionized species. The proportion depends on the pH of the medium and the pKa (the pH at which an acid or base is half ionized). The ionization of urinary excreted acids or bases is hence influenced by the urinary pH, and reabsorption can be enhanced or decreased with corresponding toxicity. Uncharged molecules are reabsorbed whereas ionized forms are excreted. If antacids that are absorbed are taken concurrently with an organic amine the latter's absorption will be enhanced. Sodium bicarbonate intake will increase the reabsorption of amphetamine. By the same token antacids will promote the reabsorption of quinidine, and acetazolamide, which makes the urine alkaline, will have the same effect. The pH partition theory also explains why basic drugs such as erythromycin are present in milk (Catz and Giacoia, 1972).

There are separate active transport processes for the renal tubule secretion of anions and cations and

competition by like-charged drugs occurs for these transport mechanisms. Acidic drugs can inhibit uric acid secretion and provoke gout.

Protein binding

Certain drugs such as the alkylating agents bind co-valently to natural polymers in an indiscriminant way unrelated to specific receptor sites. Acylation is a feature of the β -lactam antibiotics and the co-valent linkage with proteins is the chemical lesion responsible for allergenicity. Acetylation of natural polymers is believed to account for some of the ill effects of aspirin. Salicylates have been made without the offending acetyl group, such as diflunisal.

The principal binding plasma protein is albumin and at a pH of 7.4 has a negative charge but it can still react with anions and cations (Stenlake, 1979) and the drugs with the greatest affinity for albumin are organic anions such as phenylbutazone and warfarin. Albumin is also quantitatively the most important binding protein for neutral molecules (Lindup and Orme, 1981). Bases are believed to be bound to globulins and to an α_1 -acid glycoprotein (Lindup and Orme, 1981). Drugs which are acidic, lipophilic or possess long chains can displace other drugs. Most drugs are bonded electrostatically; non-ionized drugs are bound by hydrogen bonding, Van der Waals forces and hydrophobic interactions. The amount of free and bound drugs alters if the pH of the blood changes as in 'acidaemia' and this can have clinically important consequences. When strongly acidic agents displace bound drugs they temporarily raise the level of free drug. Interference with protein binding can cause spurious laboratory tests as when fenclofenac displaces thyroxine (Taylor *et al.*, 1980).

Isomers

Isomers differ in toxicity as is the case with D and L-penicillamine. Pharmacokinetic responses may differ as well between isomers. The 2 stereoisomers of warfarin the *R* and *S* forms are dealt with metabolically in different ways: the *S*(—) enantiomer is 7-hydroxylated and is more potent and has a longer half-life than the *R*(+) isomer which is changed to warfarin alcohol. Phenylbutazone stereospecifically inhibits the metabolism of the more powerful *S*(—) form and this is more likely the basis for the harmful interaction than drug-protein displacement.

Bioavailability

Pharmaceutic difficulties arise from many reasons relating to solubility, dissolution, disintegration and chelation and have been extensively reviewed elsewhere; side effects are caused by differences in formulation of drugs (Groves, 1979).

References

- ARIËNS, E.J. (1980) Design of safer chemicals. In: *Drug Design vol. IX* (Ed by Ariëns, E.J.), pp. 1–44. Academic Press, New York.
- ARIËNS, E.J. & SIMONIS, A.M. (1979) Safer drugs for a safer medicine. In: *Towards Better Safety of Drugs and Pharmaceutical Products* (Ed by Breimer, D.D.), p. 3. Elsevier North Holland Biochemical Press, Amsterdam.
- BOYLAND, E. (1980) The history and future of chemical carcinogenesis. *British Medical Bulletin*, **36**, 5.
- CATZ, C.S. & GIACOIA, G.P. (1972) Drugs and breast milk. *Pediatric Clinics of North America*, **19**, 151.
- CONNORS, T.A. (1979) The induction of cancer by drug therapy. In: *Drug Toxicity* (Ed by Gorrod, J.W.), p. 161. Taylor and Francis Ltd, London.
- GOLDMAN, P. (1980) Metronidazole. *New England Journal of Medicine*, **303**, 1212.
- GROVES, M.J. (1979) Side effects caused by differences in formulation of drugs. In: *Drug Toxicity* (Ed by Gorrod, J.W.), p. 101. Taylor and Francis Ltd, London.
- LINDUP, W.E. & ORME, M.C.L'E. (1981) Clinical pharmacology. Plasma protein binding of drugs. *British Medical Journal*, **282**, 212.
- SELKIRK, J.K. (1980) Chemical carcinogenesis. In: *The Basis of Medicinal Chemistry*. 4th edn, Part I. (Ed by Wolff, M.E.), p. 455. John Wiley and Sons, New York.
- STENLAKE, J.B. (1979) *Foundations of Molecular Pharmacology Vol. 2. The Chemical Basis of Drug Action*. The Athlone Press, University of London.
- TAYLOR, R., CLARK, F., GRIFFITHS, I.D. & WEEKE, J. (1980) Prospective study of effect of fenclofenac on thyroid function tests. *British Medical Journal*, **282**, 911.
- VENITT, S. (1980) Bacterial mutation as an indicator of carcinogenicity. *British Medical Bulletin*, **36**, 57.
- YALKOWSKY, S.H. & MOROZOWICH, W. (1980) The physical chemical basis for the design of orally active prodrugs. In: *Drug Design Vol. IX* (Ed by Ariëns, E.J.), p. 122. Academic Press, New York, London, Toronto, Sydney, San Francisco.