Drug toxicity

Edited by J.W. Gorrod

DRUG TOXICITY

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Preface

J. W. Gorrod

The material contained in this volume was originally presented at the Pharmaceutical Society's Easter School in April 1978 on Aspects of Drug Toxicity. The lecturers at this school were all experts in their topics, which were chosen to present as wide a view as possible of the contemporary situation of drug toxicity. In a volume of this size, it is not possible to cover every aspect of the subject, but it is hoped that the data presented will enable practising pharmacists and others to assess the likelihood of an adverse reaction having occurred, to propose mechanisms for its initiation, and to suggest means for preventing toxic reactions.

This volume is a sister volume to *Drug Metabolism in Man* and basic data presented in the earlier book have generally been omitted from this one. The first chapter deals with metabolic processes which are available, and for which evidence exists as toxication reactions (Gorrod). This is followed by chapters indicating how these reactions can be modified due to physiological or pharmacological factors. Amongst the topics considered are age (Jondorf), diet (Greaves & McClean), genetics (Boobis). Then follows a chapter on the influence of drug formulation or drug toxicity (Groves). Parke then considers the toxicological consequences produced via enzyme induction or inhibition and Connors deals with the possibility of neoplasia being produced during drug therapy.

Other authors then deal with the effect of drugs and foreign compounds on specific organs or systems. The organs covered are the liver (Slater), the lung (Orme), blood and blood-forming systems (Girdwood), the nervous system (Marsden & Jenner), the foetus (Beck), the optical system (Bron) and the skin (Felix).

Levene presents data which show how chemicals toxic to connective tissue have the potential to be developed into useful drugs. The last chapter deals with untoward effects which may be found during treatment with radiopharmaceuticals (Keeling).

As we live in a world where we are increasingly exposed to small amounts of chemicals in our environment and in our food and drink, the implications of much of this material go far beyond drugs. During the last decade, increasing demands have been made on manufacturers to provide materials

which are 'safe'. It is hoped that this volume will help newcomers to the field of toxicology, in that it provides a broad-based basic text, that nevertheless points to the direction in which toxicology is now rapidly moving.

It is a pleasure to record the encouragement I have received from Professor A. H. Beckett, Head of the School of Pharmacy, Chelsea College, the representatives of the Pharmaceutical Society and the contributors.

It was again a pleasure working with Dr. J. Cheney of Taylor & Francis whose expertise made my lot that much easier.

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This volume is dedicated to

E. Boyland, D.Sc.
Professor Emeritus of the University of London

whose recognition of epoxides as active metabolites
paved the way for recent developments
in molecular toxicology

Contents

1. Toxic products produced during metabolism of drugs and foreign compounds

J. W. Gorrod

Introduction

In order for a compound to produce a deleterious effect upon a biological system, a reaction between the compound, or a substance derived from it, and a component of the biological system must occur. These reactions may be proximate, i.e. acting at a site directly involved in the advent of the toxic response or they may occur by reacting with a component involved in a sequence of biochemical processes, the disturbance of which precipitates the toxic crisis (Table 1.1). Even within these groups, the nature of the chemical

Table 1.1. Examples of toxicants acting via a direct or indirect reaction within cell.

Toxicant	Reaction	Consequences
Direct reaction		
Cyanide	Complexes with Cytochrome	Block Oxidative Phosphorylation & Respiration
Phenylhydroxylamine	Oxidizes Haemoglobin	Prevents Oxygen Transport
Fluorocitrate	Inhibits Aconitase	Blocks T.C.A Cycle
6-Aminonicotinamide	Forms analogues of coenzymes	Blocks Pentose Pathway
Indirect reaction		
Silica	Absorbed into lyosomes	Releases hydrolytic enzymes
Free Radicals	React with lipids	Initiate lipid peroxidation
Mercurials	React with thiols	Removes protection and upsets cell oxidn/redn. potential

reaction is often poorly defined and whilst in many cases evidence has been obtained for the formation of covalent bonds between toxicants and cellular constituents, this is by no means a prerequisite for a toxic response. In other cases, reaction via an ionic band or a charge-transfer complex may play a role in initiating an adverse response to a drug. Thus the ability of a compound to react with an enzyme or a membrane or a discrete molecule may arise by several mechanisms.

The nature of the bond formed is important in determining the duration

of the compounds within the body; in certain cases the bond may be easily destroyed, as in the dissociation of certain inhibitors from enzymes or by hydrolysis, as in the breakdown of Schiff bases. The alternative situation may occur where the covalent bond formed between a toxicant and a macromolecule is extremely stable and only excision of the affected portion of molecule allows the release of the toxicant.

While the majority of compounds which are able to produce toxic effects require metabolism in order to produce a more reactive molecule, this is not always the case, and many molecules which are used in human therapy possess an inherent reactivity which allows reaction with cellular components. Examples of this type include various alkylating agents, including those based on strained rings, cyclic lactones and lactams. Some structures of this type of reactive compound are shown in Figure 1.1. This reactivity may enable drugs to produce antigenic material by reaction with protein and thereby produce an unwanted immunological response (Erlanger, 1973).

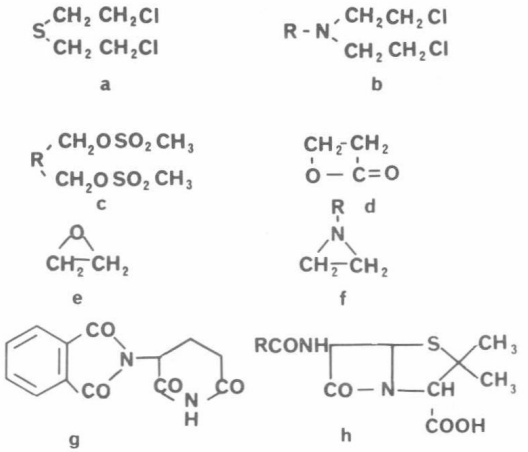

Fig. 1.1. Examples of chemically reactive drugs (*a*) sulphur mustards, (*b*) nitrogen mustards, (*c*) methylsulphonyl esters, (*d*) propiolactone, (*e*) ethylene oxide, (*f*) ethyleneimines, (*g*) thalidomide, (*h*) penicillanic acid.

Most of the toxic compounds to which we are exposed consist of carbon in combination with a hetero atom, usually oxygen, nitrogen or sulphur, and during metabolism either the carbon, nitrogen or sulphur is attacked. It is worth considering toxic metabolites produced by these processes separately.

Toxic metabolites produced via metabolic attack on carbon

Due to the potent carcinogenic properties of a number of polycyclic aromatic hydrocarbons, this group of compounds have been extensively studied over nearly half a century, Kennaway (1930) having isolated and characterized the first pure carcinogens as aromatic hydrocarbons. It was early recognized the dihydrodiols were formed as metabolites of aromatic hydrocarbons (Boyland & Levi, 1935; Young, 1947; Boyland & Wolf,

1950), a fact that led Boyland (1950) to suggest that aryl epoxides were intermediates in the metabolism of hydrocarbons. It was not until the successful synthesis of this type of compound had been accomplished by Newman & Blum (1964) that aryl epoxides were shown to exist; this ultimately led to the direct detection of naphthalene-1,2-epoxide as a metabolite of naphthalene by Jerina *et al.* (1968).

Aryl epoxides, as predicted by Boyland, are compounds capable of several reactions; these are exemplified in Figure 1.2. Aryl epoxides can isomerize to give phenols, the phenol formed depending upon the electron density of the carbon atoms involved, they can react with water, as substrates for the enzyme epoxide hydrase, or they can react with nucleophiles.

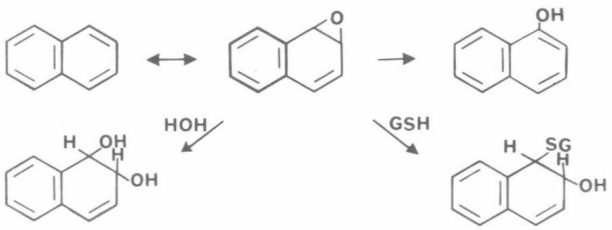

Fig. 1.2. Metabolism of naphthalene.

Figure 1.2 shows reaction with glutathione, and this type of reaction is thought to occur when epoxides react with cellular macromolecules of protein, DNA or RNA. *In vivo* glutathione conjugates are ultimately excreted as mercapturic acids. Aryl epoxides can also be reduced to the parent hydrocarbon. The role of epoxides in aromatic hydrocarbon metabolism and carcinogenesis has been reviewed by Sims & Grover (1974).

The role of epoxides in hydrocarbon metabolism becomes even more complicated when one considers the number of possible sites available for epoxidation in the larger molecules which are of major toxicological interest. An example of this complexity is indicated in Figure 1.3, which shows the three primary sites of oxidation of benzanthracene. These epoxides, viz. 5:6, 8:9 and 10:11, all react with water to form dihydrodiols as well as form analogous products as described for naphthalene earlier. There have been many attempts to correlate the site of oxidation within the hydrocarbon with the initiation of carcinogenesis, the most widely accepted being the K region hypothesis (Pullman & Pullman, 1955). However there were always anomalies and it was a major breakthrough when Swaizland *et al.* (1974) established that further epoxidation of 8,9-dihydro-8,9-dihydroxybenzanthracene was involved in the reaction of the parent hydrocarbon with nucleic acids (Figure 1.3). A similar reaction was observed with benzpyrene (Sims *et al.*, 1974). These diol-epoxides which are produced are also substrates for epoxide hydrase, being converted to tetrahydrotetrols (Figure 1.3). Many diol-epoxides are now known to be intermediates in the reaction of hydrocarbons with nucleic acids. From Figure 1.3 it can be seen that several diol-epoxides could be formed from each hydrocarbon, and while this may be the case, it appears that epoxidation of a double bond in a

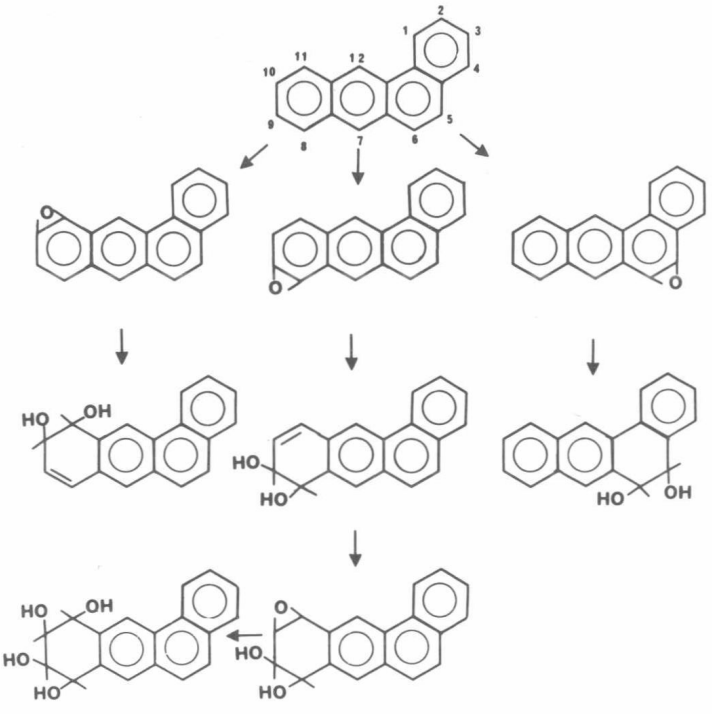

Fig. 1.3. Metabolism of benzanthracene.

diol-containing ring which is adjacent to a 'bay' in the molecule (indicated ↷ in Figure 1.4) produces the most reactive metabolite.

From a consideration of the data on the carcinogenicity of substituted hydrocarbons and quantum mechanical calculations, a theory has been developed predicting that bay region epoxides derived from non-K-region dihydrodiols would have the highest biological activity (Jerina & Daly, 1977; Jerina *et al.*, 1977). Further examples of diol-epoxides derived from carcinogenic hydrocarbons are shown in Figure 1.4.

Epoxidation as a toxication process is not restricted to aromatic hydrocarbons and it has been suggested that they are formed during the metabolism of safrole (Figure 1.5A). In the case of this weak carcinogen, it is not certain whether hydroxylation of the methylene carbon is also required to produce the proximate carcinogen (Stilwell *et al.*, 1974). Aflatoxin B_1, which is a potent naturally occurring carcinogen, is also thought to be activated via epoxidation of the distal furan ring (Figure 1.5B) (Swenson, Miller & Miller, 1974). Epoxidation may also be involved in the toxic effects produced by vinyl chloride.

From the foregoing it might be presumed that epoxidation was always associated with enhanced toxicity. However, studies using epoxides known to be formed as metabolites of carbamazepine, cyproheptadine and cyclobenzaprine (Figure 1.6) showed that they were fully devoid of mutagenic activity when tested in systems capable of detecting either frameshift or

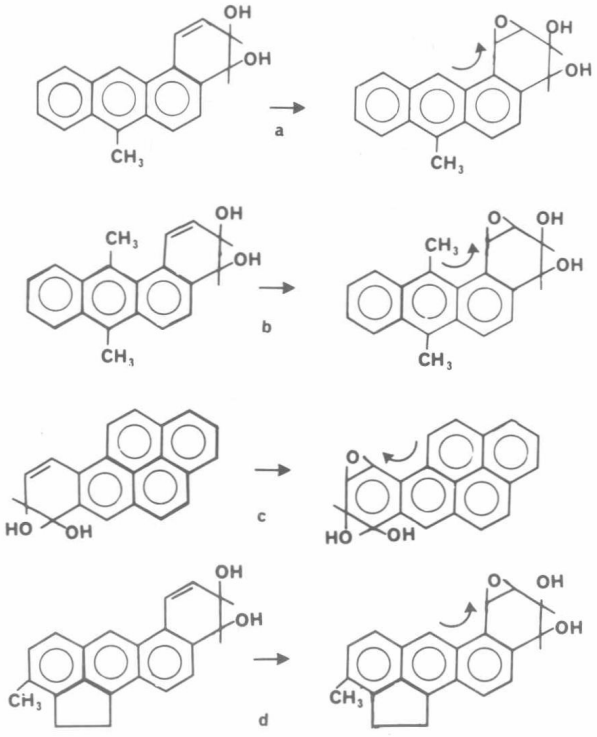

Fig. 1.4 Conversion of (*a*) 7-methylbenzanthracene, (*b*) 7, 12 dimethylbenzanthracene, (*c*) benzpyrene, (*d*) methylcholanthrene, to 'bay region' epoxides.

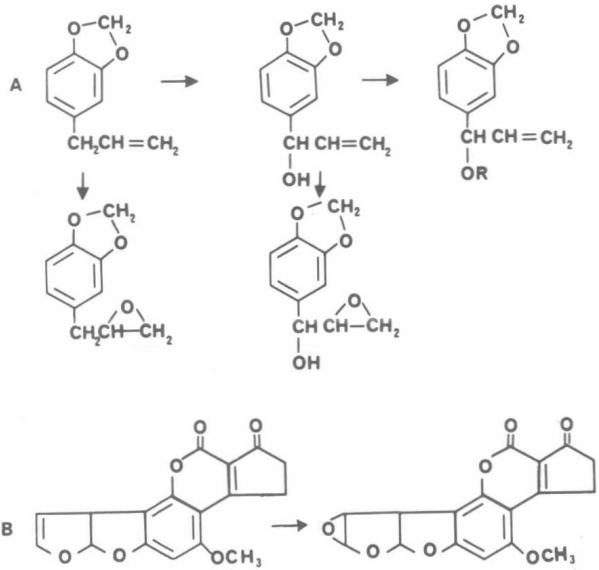

Fig. 1.5 Metabolism of (A) safrole and (B) of aflatoxin to form epoxides.

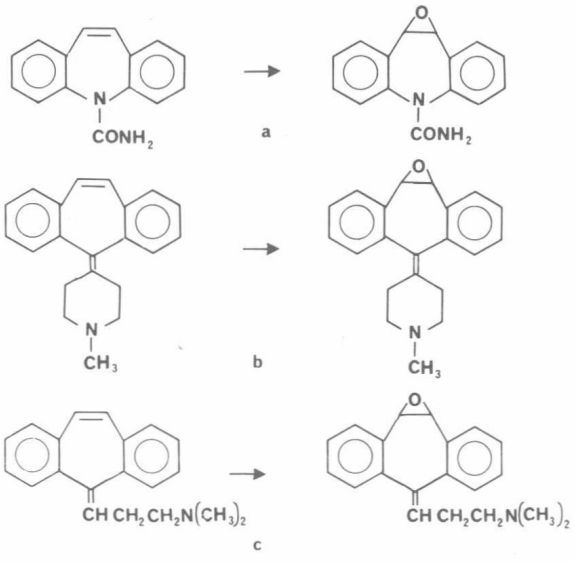

Fig. 1.6. Epoxidation of drugs containing an aliphatic double band.

base substitution mutagens (Glatt *et al.*, 1975). Indeed, studies on the metabolism of the hepatotoxic agent bromobenzene (Figure 1.7) (Jollow & Smith, 1977) suggest that whereas pretreatment of experimental animals with phenobarbitone produces more bromobenzene-3,4-epoxide, leading to enhanced toxicity, pretreatment with methylcholanthrene leads to more 2,3-epoxide, leading to diminished toxicity as the toxic 3,4-epoxide is formed in

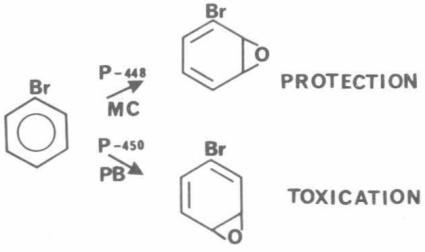

Fig. 1.7. Possible metabolic conversion of bromobenzene to two different epoxides.

lower amounts. Clearly epoxidation can be a reaction which is involved in producing a toxic effect. However, the variety of further reactions which epoxides can undergo (Figure 1.2) and the rate at which these reactions proceed, will determine the role of epoxides in the metabolism and toxicity of any molecule. As the site of epoxidation and the properties of the epoxide formed are dependent upon the electron distribution within the molecule and the activity of the various P-450-type cytochromes and the environment within which they are formed, it may be that in many cases the potential toxic effect is never realized or only manifests itself under certain conditions.