Drug Reactions and the Liver

Edited by
Michael Davis
J Michael Tredger
Roger Williams

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Michael Davis MD MRCP
Honorary Consultant Physician, The Liver Unit, King's College Hospital and Medical School, London

J Michael Tredger PhD
Lecturer in Biochemistry, The Liver Unit, King's College Hospital and Medical School, London

Roger Williams MD FRCP
Consultant Physician and Director of the Liver Unit, King's College Hospital and Medical School, London

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PREFACE

This book stems from the proceedings of an international symposium held at the Royal Society, London, in July 1980. The spectrum of hepatic abnormalities which can complicate the use of therapeutic agents continues to broaden, but in only a few instances is there a clue as to the underlying pathogenesis. Over the past decade, much has been learned about the role of reactive metabolites in the generation of liver injury, and while this has led to important therapeutic advances, notably the development of protective agents to prevent paracetamol-induced hepatic necrosis, for most drugs there has been little progress in linking the results of laboratory studies to the illness in the patient. The need for a broader scientific approach is evident, and in organising the programme our aim was to co-ordinate the various approaches of clinicians, basic scientists and members of the pharmaceutical industry in the hope that, from the open dialogue which ensued, new perspectives would emerge. Much of the meeting was given over to panel discussions, which were loosely structured in advance to allow as many presentations as possible of different points of view.

To bring together so many participants from so far afield involved considerable effort as well as expense, and we are most grateful to Ciba Geigy Pharmaceuticals and to Dr Ralph Kohn and his team at Advisory Services Medical Symposia Limited for making the onerous task of organising this meeting so easy for us.

We are also indebted to Dr Mary Firth for her expert transcription of the discussion periods, and to Mrs Betty Dickens of Pitman Medical for all her help in the preparation of this book.

Michael Davis
J Michael Tredger
Roger Williams

FOREWORD

For a variety of reasons, the response of the liver to drugs and chemicals is becoming a growing concern to an increasing part of the population. As more potent drugs are being developed, adverse effects in various organs, including the liver, limit their use. Thus, surveillance after the drug has been released for general use is now emphasised, supplementing the study of its hepatotoxic potential in animals and its initial evaluation in man. The reasons are non-predictable, sometimes fatal reactions which could not be expected from animal studies and from initial evaluations in man. Moreover, in patients with established liver disease with or without jaundice the question arises more and more frequently whether a drug is responsible for or contributing to the disease. In older people, drug-induced injuries are frequent. This is particularly important because withdrawal of the responsible agent is one of the few examples of rational therapy in liver diseases. Furthermore, the awakening concern with environmental factors has raised the spectre of hidden intoxications, with long-term exposure to small doses as the cause of various human diseases of so far unknown aetiology. This possibility is illustrated by the claim that the majority of human cancer is of environmental origin and some groups emphasise, possibly unduly, industrial exposure. Thus, the promise is held out that the recognition and elimination of hidden intoxications may reduce the cancer burden of mankind. Finally, the study of the response of the liver to drugs has provided considerable information as to the reaction of this organ to injury in general, and the pharmacologic dissection of disease processes has widened the knowledge of pathobiology. The genetic influences on drug reactions are a telling example.

It is therefore not astonishing that drug reactions of the liver attract the interest not only of the biomedical professional, of the pharmacologist and of the basic scientist but especially of the physician caring for the individual patient, who has to recognise the cause of the disease or to weigh the risk/benefit ratio in using a potentially hepatotoxic drug. In addition adverse reactions are also of overriding importance to the pharmaceutical industry, its scientists and its managers, at a time when the cost of developing a drug is skyrocketing. The possibility of industrial injury has extended this interest to the entire chemical industry. Last but not least, the population at large and the government as its arm are now alerted to the potential dangers and the regulatory

agencies have to make difficult but responsible decisions.

Many available books and review articles discuss these problems, but the attempt to cover at one symposium all the different aspects and to obtain a consensus has been seldom made. This symposium and this publication try to fulfil this aim. The result has been a critical review of available information and restatements of opinions of all the groups listed. It provides also, to a surprising degree, new observations not recorded before. Worthy of emphasis is the emerging recognition that the variations in susceptibility to drug reactions may be explained by individual differences both in metabolic transformation of the chemical and in immunologic reactions to it, that both processes may interact, and that both are genetically determined. Further progress along this line may reduce the hazards of drug therapy by identifying the person at risk. Hopefully, this may in time eliminate many of the unforeseen adverse reactions.

The reader will thus find an up-to-date review of the most important adverse hepatic drug reactions, of their pathogenesis, and of the present status of toxicity testing and screening, but he may be even more interested in the interaction between physicians, basic scientists, and representatives of industry and of regulatory governmental agencies. Let me close with an appreciation to all those who made this symposium possible, an appreciation which I hope the reader will share.

Hans Popper

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INTRODUCTION

Roger Williams, J Michael Tredger, Michael Davis

The Liver Unit, King's College Hospital and Medical School, London, United Kingdom

The importance of drug-induced liver injury reflects not only the increasing number of therapeutic agents whose potential toxicity has been recognised, but also a growing awareness of the wide spectrum of hepatic abnormalities they may produce (Table I). This extends far beyond the classical lesions of acute hepatitis and cholestasis, and now encompasses chronic hepatitis, cirrhosis and even liver tumours [1]. Indeed, drugs have been implicated in the whole clinical and pathological range of liver injury.

TABLE I. Spectrum of drug-induced hepatic damage

1. Interference with hepatic bilirubin uptake, conjugation and excretion
2. Cholelithiasis
3. Dose dependent reactions:
   (a) Acute toxic hepatitis
   (b) Fatty liver
4. Dose independent reactions:
   (a) Diffuse hepatocellular damage
   (b) Cholestatic hepatitis
   (c) Granulomatous infiltration
5. Fibrotic lesions and chronic hepatitis
6. Liver tumours and peliosis hepatis

The last decade has seen many changes in our ideas on pathogenesis, and the classical distinction between predictable and idiosyncratic drug hepatotoxicity has become far less clear cut with the recognition that some drugs associated with the latter type of reaction cause mild abnormalities in liver function with high frequency, if these are looked for [2]. Some therapeutic agents, it is now known,

can undergo transformation to chemically reactive, hepatotoxic metabolites, although much needs to be learned about how such metabolites lead to liver injury. Not only has the production of reactive metabolites been associated with dose dependent (predictable) liver injury from agents such as paracetamol [3], but also with injury from drugs such as isoniazid [4], methyldopa [5] and halothane [6], where there is no clear relationship between dose and the appearance of hepatic damage.

Consequently, a capacity to generate reactive metabolites must be of key importance in determining the hepatotoxic potential of a drug, but the expression of liver damage in an individual must depend on many factors other than dose. These include variations in the rate and route of metabolism, and here both the genetic make-up of the individual and environmental factors are likely to be important. The relationship between acetylator status and susceptibility to adverse reactions from isoniazid [4] and hydralazine [7] are examples of how a knowledge of genetically determined differences in drug handling may be of predictive value. Much also has been learned from experimental studies of how environmentally induced changes in the metabolism of drugs can regulate their toxic potential, and especially the role of enzyme induction and diet. However, it is more difficult to quantitate the importance of such influences in the clinical situation.

The place and significance of immunological mechanisms in certain hepatic drug reactions is also uncertain. Although clinically many appear to be manifestations of hypersensitivity, the results of testing for sensitisation to drugs in isolation have been largely inconclusive. However, the awareness that some such compounds produce unstable metabolites which could alter the antigenicity of hepatocyte components [8] has opened new avenues for investigation. Individual differences in immune responsiveness to drug altered liver antigens represent yet another determinant of susceptibility which may need to be considered.

Susceptibility to drug induced liver injury must therefore result from a complex interplay of genetic and environmental factors, and in the future we may need to pay more attention to adjusting drug dosage to provide each individual patient with optimum therapeutic efficacy with the minimum risk of side effects.

Clearly a multidisciplinary approach to the problem is now called for to achieve the necessary perspective, and this meeting was planned to encourage such an exchange and address ourselves to the following questions:

(1) How do the metabolic and immunological events observed experimentally relate to the pathogenesis in man?

(2) How can we predict those patients at particular risk and the likely severity of a reaction?

(3) How can we prevent the ever increasing complexity, and therefore costs of screening for hepatotoxicity, from acting as too great a deterrent to the pharmaceutical industry in its search for new compounds?

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THE REPORTING OF DRUG REACTIONS: VALUES AND LIMITATIONS

C T Dollery

Department of Clinical Pharmacology, Royal Postgraduate Medical School, London, United Kingdom

The concept of highly specific drug therapy originated with Paul Ehrlich. He spoke of a silver bullet with magical properties that would destroy diseased tissue while leaving the normal cells unharmed. Unfortunately Ehrlich's silver bullet sometimes turns out to have a dirty lead-grey lining of unacceptable toxicity.

Drug toxicity has received increasing emphasis for three main reasons. The first is related to the availability of alternative treatments for many common diseases. Given comparable efficacy, the least toxic treatment is preferred. Finding out which is the least toxic has therefore become an important objective of therapeutic research. The second reason has been the extension of prolonged drug therapy to patients with less severe manifestations of some common diseases, e.g. hypertension, diabetes, arthritis. Prolonged exposure increases the likelihood of toxicity and in mild disease it is less acceptable. Several recent episodes of drug toxicity would never have occurred if the drugs had been given for only short periods, e.g. clioquinol and practolol [1, 2]. The third reason is related to the current public awareness of environmental pollution and so called 'green politics'. In consequence problems of drug toxicity often have to be discussed publicly when the extent, and sometimes even the existence, of the problem is not well defined. The benefits of drug therapy are rarely taken into account in these discussions.

Thus the problem of drug toxicity is not solely one of detection. Accurate assessment of the incidence and severity is also extremely important. Just as generals are said to fight the first battles of a new war using the tactics which were appropriate to the last one, so the methodology of animal toxicity tests and human adverse reaction detection is strongly, perhaps excessively, influenced by past episodes of toxicity. There is also the problem of relating costs to benefit. Efficient methods of detecting low frequency toxic events are likely to be expensive. Complexity and cost probably make it impractical to establish surveillance systems which are capable of detecting serious toxic events that occur in a frequency of less than about one in 1,000 patients treated.

Methods of adverse reaction detection

Doctor-induced disease is now a common problem. Drugs are the usual cause of doctor-induced disease. Many of the problems caused by drugs are related to their known pharmacological actions and thus are to a large extent predictable. These adverse reactions are usually termed side effects and they range from the trivial, such as the blocked nose in a patient on propranolol, to the life-threatening such as bone marrow failure or a chemical cystitis in a patient on cyclophosphamide. The term drug toxicity is usually restricted to unexpected events which are not directly related to the known actions of the drug. In many ways this is a false distinction but it is convenient for limiting the magnitude of the present discussion. How are such toxic events usually detected?

Clinical suspicion

The most effective means of detecting drug toxicity is for the physician in charge of the patient to suspect it. If that physician is a specialist who sees referrals of a particular type of disease from a large population, his chances of detecting a low frequency event with an unusual presentation may be remarkably high. Most of the known types of toxicity were first detected in this way, e.g. thalidomide by obstetricians and paediatricians [3], practolol by dermatologists and ophthalmologists [2], aminorex pulmonary hypertension by cardiologists [4]. It would be unwise to forget amidst all the discussion of more structured systems of post-marketing surveillance that this is still our chief defence. Often such suspicions first see the light of day in the correspondence columns of the weekly journals such as the Lancet. Letters reporting such events can pose problems for referees because if they are true they are very important but if they are not true they can cause a great deal of unnecessary alarm amongst a large number of patients and their doctors. But as a way of first expressing a clinical suspicion they are unrivalled.

Voluntary reporting systems

Voluntary reporting systems represent an extension of individual clinical suspicion by encouraging large numbers of doctors to report untoward events that they suspect may be caused by a drug. Instead of the association of ideas taking place solely in the mind of one doctor in a special clinic it may take place in the National Agency for co-ordinating adverse reaction reports who can evaluate the profile of reports in each particular category. This method too has had its successes such as the early detection of jaundice caused by ibufenac and the evaluation of the relationship between dose and the incidence of thrombo-embolism in patients taking the contraceptive pill [5, 6]. Unfortunately the spontaneous reaction warning system in the United Kingdom failed to detect practolol toxicity presum-

ably because physicians did not suspect that the skin and eye changes were related to a drug [7].

Under-reporting is another serious problem. The secretariat of the Adverse Reactions Branch of the Committee on Safety of Medicines have carried out assessments of the completeness of spontaneous reports by analysis of death certificates. These studies have shown very heavy under-reporting even of fatal adverse reactions to drugs (about one in ten) [8].

Changes in national mortality figures

If a country has an accurate national death certification system these statistics can be used to monitor changes in mortality experience. Small changes in the number of uncommon causes of death, such as bladder cancer, or larger changes in common diseases such as asthma may provide the lead for an investigation of a problem of drug toxicity. The epidemic of asthma deaths that took place in Britain and some other countries between 1960 and 1967 was detected in this manner [9, 10]. This method is limited by the accuracy and completeness of death certificates as well as the magnitude of the increase in relation to the background incidence of the specific cause of death under study.

Post-marketing surveillance

The alternative to systems that rely on clinical suspicion and voluntary reports is direct monitoring of individuals exposed to drugs. One of the best known examples of such a system is the Boston Collaborative Drug Surveillance Program [11, 12]. This programme uses nurse monitors who interrogate patients admitted to hospital about drug therapy, personal characteristics, diagnoses and incidents that might be adverse effects of drugs. The problem with such a system is that it is relatively costly and the population monitored is entirely hospital based (and largely North American). Various alternative schemes have been proposed which would involve monitoring much larger numbers, either of patients on one specific drug or a whole community of patients taking a variety of drugs. Such systems of surveillance involve two main steps, registration and monitoring.

Registration

Specific monitoring is impossible unless the identity of a patient starting treatment with a drug can be accurately recorded. There are several possible ways of achieving this end. One is to ask doctors or pharmacists to register the names of patients who have been receiving prescriptions for a named drug. Such systems can be effective but they are prone to suffer from incomplete recording. Systems which do not involve additional work for medical, nursing or pharmaceutical staff seem preferable. Such information might be retrieved by computers from hospital discharge

summaries or, in the United Kingdom, from the National Health Service Prescription Pricing Authority.

The registration step has received most attention from students of adverse reactions because it presents less difficulties than the second step, monitoring.

Monitoring

There are two main ways of using a registered population. The simplest would be to use it only to confirm and quantify suspicions that have originated elsewhere. This in itself might be very valuable. No specific action would be required unless a suspicion was aroused in which case the doctors looking after the patients on the suspect drug would be asked to complete a questionnaire, and possibly also to loan their records for abstraction of information. If necessary the patients could themselves be recalled, interviewed and examined.

However more ambitious schemes of monitoring set themselves the objective of detecting adverse reactions rather than simply confirming and quantifying them. Several different methods of data acquisition have been proposed. The most straightforward is to ask the doctor in charge of the patient to fill in a form at intervals which indicates all new diagnoses that are made, hospital admissions and consultant referrals [13]. Perhaps the most important question is 'Why did you stop drug X?' It is uncertain how much co-operation will be obtainable from the generality of the family practitioners if such enquiries become frequent. A second possibility is to ask the patient to fill in a more detailed questionnaire concerning symptoms that they may have suffered [14]. Some doctors regard this as a controversial proposal but it might increase the sensitivity for detecting adverse events.

Experience of registration and monitoring systems is limited and there is no success to point to as is the case with the longer established methods. In my opinion, it would be wise to experiment with this method by monitoring a small number of drugs that are new chemical entities (NCE) before adopting a general system of monitoring such as that proposed by the Committee on Safety of Medicines. Even if a reasonably complete record of events suffered by patients taking an NCE can be compiled there will still be great difficulties in interpretation.

Randomised controlled clinical trials (RCTs)

RCTs are normally undertaken to provide evidence of efficacy. Less attention has been paid to their usefulness as a source of information about side effects and toxicity. Yet if the trial is designed to yield such information it is likely to be of much higher quality than that available from other sources because of the existence of a randomly allocated control group. The data is particularly valuable if the control group received a placebo rather than another active drug. The Medical Research Council's Hypertension Trial is a good example. By collecting information about withdrawal from randomised treatment and administering symptom ques-