Stephens

The Detection of New Adverse Drug Reactions

SECOND EDITION
Revised and Updated

The Detection of New Adverse Drug Reactions

M.D.B. Stephens
with a guest chapter contributed by
J.C.C. Talbot

and
contributions on drug regulations
from

Dr B. Bons
Dr J. Dobbs
Dr M. Hadoke
Dr M. Kurihara
Dr G. Recchia
Dr J.C.C. Talbot

Second edition

First edition 1985
Reprinted 1986
Second edition 1988

Published by
THE MACMILLAN PRESS LTD
Houndmills, Basingstoke, Hampshire RG21 2XS
and London
Companies and representatives throughout the world

Typeset in 10 pt Century by Medimedia, Godalming, Surrey
Printed in Hong Kong

British Library Cataloguing in Publication Data
Stephens, M.D.B.
The detection of new adverse drug reactions.—2nd ed.
1. Drugs—Side effects
I. Title II. Talbot, J.C.C.
615'.704 RM302.5
ISBN 0–333–45417–0

Published in the United States and Canada by
Stockton Press
15 East 26th Street, New York, NY 10010

Library of Congress Cataloguing in Publication Data
Stephens, M.D.B., 1930–
The detection of new adverse drug reactions.
Bibliography: p.
Includes index.
1. Drugs—Side effects. 2. Drugs—Toxicology.
I. Talbot, J.C.C. II Title.
RM302.5.S74 1985 615'.7042 85–2834
ISBN 0–935859–49–7

Foreword

We stand on the threshold of what has been called 'the second pharmacological revolution'. During the past three decades major therapeutic advances have been made, but they may well be overshadowed by those of the rest of the century, as new molecular biochemical discoveries, and techniques for genetic engineering, permit control of viral, psychiatric, malignant and autoimmune disease. Tragically, however, this optimistic prediction is threatened by ill-advised yet widespread public fear of, and indeed hostility to, new drugs, fostered by a variety of consumer and media lobbies who have not yet understood that a chemical's therapeutic efficacy is inevitably associated with unwanted effects, particularly if used unwisely.

Many books have been written about the design of clinical trials and determination of therapeutic efficacy of drugs, but little has been published on the systematic detection, quantification and evaluation of adverse drug reactions. This process should begin, of course, with the earliest administration of a drug to man, and continue throughout its controlled clinical trials, but is likely only to identify relatively common or bizarre adverse effects. Less common, but nevertheless important, unwanted effects will be recognised only when it is prescribed for larger numbers of patients, usually after it has been marketed, and when its use, therefore, is less closely supervised.

Dr Stephens has been closely involved in the practical problems of adverse drug reaction monitoring for many years, and this book represents an important contribution to the subject which I believe will be of value to all involved in the scientific assessment of drug treatment.

Professor Paul Turner, MD, BSc, FRCP
Department of Clinical Pharmacology
St Bartholomew's Hospital Medical School
London

Preface to the First Edition

This book sets out to describe the problems involved in the detection of new adverse drug events both before and after a drug reaches the market and the various methods available to overcome these problems. The methods cover the collection, storage and assessment of the information. It is hoped that it will be found useful to those involved in clinical trials, whether clinical or pharmaceutical scientist. For the latter it is also hoped that he or she will find sufficient information and referenced papers to be able to set up a drug surveillance unit within a pharmaceutical company.

The withdrawal from the market of numerous drugs over the last few years has prompted changes in the regulations in many countries and, therefore, in turn has caused, and will cause, great changes within the pharmaceutical industry.

The most important change will be the realisation that equal effort and money will need to be put into both sides of the cost/benefit ratio in the clinical research of a new drug.

I have resisted the temptation to stray into the more fascinating and controversial areas, such as the law on liability and compensation for drug injury or the history of various established adverse drug reactions, but I hope that the bibliography will have covered these gaps.

All opinions mentioned in this book are my own, unless specifically stated as being otherwise. It should not be presumed that any views or practices described here are those of the Glaxo Group or any of its subsidiary companies, unless stated.

Bishop's Stortford, 1984 *M.D.B.S.*

Preface to Second Edition

Since the original edition was published in 1985 there have been a number of changes in the field of adverse drug reactions. Important changes in pharmaceutical law in several countries have brought about changes within the industry so that most large pharmaceutical companies now have a department to deal with drug surveillance.

There have been recently several Drug Information Association meetings and workshops dedicated to relevant topics, such as clinical data management, pre-marketing adverse drug experiences, data management procedures, the future of ADR diagnosis: computers, clinical judgement and the logic of uncertainty.

As a result I have rewritten the chapters on assessment of adverse medical events and post-marketing surveillance, and there is a new chapter on laboratory investigations. The chapters on methodology of the collection of adverse event data; the pre-marketing establishment of the side effect profile of a new drug; ethical problems; collection, storage, retrieval and management of ADR data and regulations have all had extensive changes in order to bring them up to date. The general expansion has resulted in almost double the number of references. In this edition any new information which has arrived after completion of the list of references has been inserted in the relevant chapter with the reference incorporated in the text. Information arriving just prior to going to press has been added after the Appendix.

Bishop's Stortford, 1988 *M.D.B.S.*

Acknowledgements

Whenever there has been need of statistical advice I have run to either D. Robinson or J. Foster at Glaxo Group Research, Ware, and evidence of this is seen in almost every chapter. Dr C. Bulpitt guided my first faltering footsteps in the world of controlled clinical trials and his influence has spread into many aspects of the book. The whole area of form design and post-marketing surveillance results from close collaboration with the late Dr J. Jackson of Clinical Data Monitoring, Glaxo Group Research, and I am deeply indebted to his help over the years.

I am very grateful to the following for updating the chapter on drug regulations:

United Kingdom	Dr J.C.C. Talbot
United States of America	Dr J. Dobbs
France	Dr B. Bons
Germany	Dr M. Hadoke
Italy	Dr G. Recchia
Japan	Dr H. Kurihara

I am also very indebted to my colleagues: Dr J. Talbot for his chapter on handling data, Ms M. Woods for indexing, Mrs B. Long for proofreading and Dr P. Meyer-Franzen.

It is also a pleasure to thank:

1. Dr Emmanueli of Farmitalia Carlo Erba for permission to publish his revised algorithm (August 1983).
2. Dr Ruskin for his two algorithms on drug-event association and drug-death association.
3. Dr J.A. Lewis of ICI and Elsevier Biomedical Press for permission to reproduce his statistical tables on the numbers of patients required for PMS.
4. Drs S.N. Ciccolunghi, P.D. Fowler and M. Chaudri for the use of the 'Ciccolunghi-Fowler-Chaudri Method'.

5. Dr B.D. Dinman and *JAMA* for permission to reproduce his tables of risk 'The reality and acceptance of risk', *JAMA*, 1980, 244(11), pp. 1226–1228. Copyright 1980, American Medical Association.
6. Dr C.J. Stevenson for help with the design of the skin ADR form.
7. Dr J. Haller, Dr J. Ward and Dr R. Amrein and the editors for permission to reproduce the table on page 136 from *Drugs and Driving*, J.F. O'Hanlon and J.J. de Gier (Eds), and also the Publishers Taylor and Francis Ltd.
8. Dr J. Levine for the details of SAFTEE.
9. Prof. D.L. Sackett, Dr R.B. Haynes and Dr P. Tugwell and the publishers Little, Brown & Co. for permission to reproduce the tables on pages 111–113 from *Clinical Epidemiology*, a basic science for clinical medicine. Copyright 1985.
10. Prof. D.M. Davies and the Oxford Press for permission to reproduce most of chapter 4, which was originally published in *Adverse Drug Reactions and Acute Poisoning Review*, 1987, **1**, 1–35.
11. Dr G. Venning and Prof. D.M. Davies for permission to reproduce the graph on page 125 which originally appeared in *Adverse Drug Reactions and Acute Poisoning Review*, 1984, **3**, 113–21.
12. Dr J.A. Tangrea for the details of the basal cell carcinoma prevention trial.
13. Dr N. Mohberg for details of the forms used in clinical trials for medical events.
14. Glaxo Group Research Ltd for permission to reproduce various forms.
15. Dr W.H.W. Inman for information concerning P.E.M.
16. Dr W. Castle for information concerning the C.I.O.M.S. form for ADR reporting.
17. The post-marketing surveillance working group of The International Federation of Pharmaceutical Manufacturer's Association (IFPMA) for the definitions of terms from an IFPMA position paper.
18. PJB Publications Ltd for permission to reproduce extracts from *Eurodrugs Step by Step*.

Contents

1
Introduction

Adverse drug reactions (ADR) must have started at the dawn of time when man first used plants as medication and learnt to brew alcohol and smoke tobacco. Both Homer (700 BC) and Hippocrates (400 BC) referred to them as problems. The history of ADR before thalidomide has been covered by Penn in *Iatrogenic Diseases* (see Bibliography).

The first important therapeutic disaster which prompted the world to demand a better system for the detection of adverse drug reactions was thalidomide phocomelia, first mentioned in *The Lancet* of 2nd December 1961[1], and this was later reinforced by the practolol disaster in 1975[2]. It has been claimed that the side effects of practolol would have been discovered much earlier, had the adverse events in the early clinical trials been reported more fully[3,4]. Present pre-marketing clinical trials often fail to discover what are subsequently known to be important side effects[5,6], as witnessed by the events with Opren (benoxaprofen) and Zomax (zomepirac). The final destination of the data collected on adverse events from pre-marketing clinical trials is the licensing authority and one of these has commented that the information on adverse effects submitted by drug companies is often of poor quality[5]. Even in early clinical trials (Phase II), not all adverse effects are reported[7].

Once a drug is marketed, only about 10% of its adverse reactions are reported[8] and there is evidence that the deaths attributable to excessive use of bronchodilating aerosols were under-reported[8,9], as were the thrombo-embolic deaths due to the pill[10,12] and the practolol eye problems[11]. The poor reporting of adverse reactions for marketed drugs is not confined to the United Kingdom. America[5], France[13] and Germany[14] have reported similar problems.

In future it will no longer be sufficient for pharmaceutical companies to plan their clinical trial programme for a new drug on the basis of showing that it is efficacious and that secondarily no adverse drug reactions were noted. The cost half of the cost/benefit ratio now demands that equal effort must be put into the active search for adverse reactions as in the search for proof of efficacy.

The Purpose of this Book

The discovery of the ADR profile of a new drug prior to marketing lies entirely within the sphere of the pharmaceutical company and, therefore, they have the responsibility for providing adequate information on a new drug. After a drug is marketed, the responsibility for extending the knowledge of the adverse reactions of a new drug spreads to all the prescribers of that drug, as well as to specific organisations set up for that purpose. The originating company, however, retains the prime responsibility for the collection of adverse reaction data for the prescribers, the assessment of its validity and informing the medical world of its evaluation.

This book reviews the methods at present used for the detection of adverse drug reactions both within and without the pharmaceutical industry and suggests improvements in methodology. The theme throughout the book is of a progressive integrated programme for the detection and evaluation of possible ADR from the time a new drug first goes into man and throughout its subsequent worldwide usage.

The Cost/Benefit Ratio

Before treating a patient, a doctor must balance the expected benefits of a drug against its potential risks, i.e. evaluate the cost/benefit ratio. The situation is similar for the licensing authority in that their decision as to whether to allow a drug to be marketed must depend on the cost/benefit ratio for the whole population at risk. It should be the pharmaceutical industry's aim to provide the information necessary such that these decisions can be made.

We now turn to the two opposing factors in the cost/benefit ratio:

1. Benefits, i.e. efficacy.
2. Cost, i.e. the side-effect liability.

The Benefits — Measurement of Efficacy

The efficacy of a drug in the treatment of a disease needs to be considered compared with three alternatives:

1. No treatment and, therefore, the natural progress of the disease.
2. Placebo, which is the same as the above plus a psychological effect, which may produce objective benefits.
3. The standard treatment for that disease. If there is more than one standard treatment, then a comparison with each may be necessary.

If we presume that the healing rate for the standard therapy is greater than the natural healing rate or that induced by placebo and take as an example a healing rate of 70% for the standard therapy, we can calculate the number of patients required in the trial. In order to be approximately 90% certain of detecting a 10% difference between the standard therapy (70%) and the new therapy (60% or 80%), we would require 600 patients. If we accept the results as an adequate indication of the drug's efficacy, would this number of patients give us an adequate indication of the safety of the drug? It should certainly be able to establish the incidence of common side effects, but what chance would one have of detecting a rare serious side effect? Presuming that the side effect is identifiable as being due to the drug and that we would be satisfied in identifying one single case, we would have only a 45% chance of finding a side effect with a true incidence of 1 in 1,000 and only a 12% chance of finding two such side effects.

The Cost — The Statistical Background to ADR

With a sample size of 5,000 patients we could be more than 99% certain of finding one case of an ADR with a true incidence rate of 1:1,000 and, if we demand more than one case on which to base a decision as to whether this drug was safe to market, then the chances of finding them diminish rapidly, there being only a 73% chance of finding four such cases in the sample of 5,000 patients. The proviso mentioned earlier that the ADR is identified as being due to the drug is, however, important. If the ADR cannot be clearly differentiated from naturally occurring disease, then the problem is formidable. For instance, if the drug produced a 10% increase in a disease with a natural incidence of 1 in 1,000, then — to be 95% certain of detecting this — we would require some 1,100,000 patients and for doubling of the incidence of the disease we would need approximately 16,000. For a given number of patients we can be more certain about a drug's efficacy than we can of its safety.

The reason for this situation is that a standard treatment nearly always means that it is efficacious in more than 10% of the population ($p_1 = 0.1$) and may even be effective in 50% of the population ($p_1 = 0.5$), the increase to 11% ($p_2 = 0.11$) or doubling to 20% ($p_2 = 0.2$) in the first instance and from 50% to 55% ($p = 0.55$) and doubling to 100% healing ($p = 1.00$) in the second instance. All these are relatively large figures compared with the adverse reactions that we would be interested in which might have, say, a background death rate of approximately 1:10,000 ($p_1 = 0.0001$) doubling due to treatment to 2:10,000 ($p_2 = 0.002$); see Table 1. The increase from 50% efficacy to 55% efficacy would need a total of 3,280 patients in the study, whilst if we wished to detect a

Table 1 Number of observations needed in each group to detect given change in proportion
Power = 80%
Significance level = 5%

p_1	p_2	n
0.5	0.55	1640
	1.00	20
0.4	0.44	2490
	0.80	30
0.3	0.33	3890
	0.60	50
0.1	0.11	15130
	0.20	240
0.01	0.011	168000
	0.020	2700
0.001	0.0011	1684000
	0.0020	23000
0.0001	0.00011	11860000
	0.0002	237000

doubling of the rate of 1:10,000 we would need 474,000. If we wished to pick up a rarity like the agranulocytosis caused by chloramphenicol, we would need 1,500,000 observations[15], and at the other end of the spectrum, if we wished to compare our new hypertensive drug against placebo and we wished to be 80% certain of finding a difference of 20 mm in blood pressure (significance level 5%), we would only need 16 patients (see Table 2).

If we can satisfy ourselves as to the safety of the drug, we can assume that numbers of patients needed to do that will have been adequate for the evaluation of the drug's efficacy in the short term. It will be obvious that absolute safety is unobtainable even in the relatively short term. The problem of the changing cost/benefit ratio in the long term is even more difficult. Practolol has introduced us to the medium-term ADR problem with a mean time to onset of eye signs of 23 months[16], whilst the delay between the use of diethylstilboestrol and the appearance of vaginal adenocarcinoma in the children of its recipients of at least 21 years[17] represents the long-term problem. The problem of long-term

Table 2 Number of observations needed in each group to detect a given difference in the group means in a parallel group trial
Power = 80%
Significance level = 5% SD = 14 (approx)

Difference in means	Number of observations
2	760
5	120
10	30
15	15
20	8

evaluation of the cost/benefit ratio has been illustrated by clofibrate where ultimately the cost has exceeded the benefits but the reasons why are not known[18,19].

It is clearly essential that maximum advantage be taken of clinical trials to establish the side effect burden of a drug and that great effort must be made to collect side effects presenting after marketing and that these must then be correctly assessed.

The Risks

Since there is no way of proving the complete safety of a new drug before it comes into widespread use, it becomes a question of when do we wish to be able to define the risks. The easy answer is: as soon as possible, so that as few patients as possible are exposed to unnecessary risks. As the number of patients increases so we can define the risks with greater accuracy and then continue until the drug is marketed, when there is no longer a 100% reporting on the fate of each patient treated. Before allowing a new drug on to the market, the regulatory authority must weigh the advantages of the efficacy of the new drug, compared with the normal prognosis of the disease with known therapy, against the risks involved in marketing the new drug without full knowledge of its adverse reaction burden. At the same time the regulatory authority must decide whether they leave the detection of the more rare side effects to be discovered by the present systems or whether they should institute a major surveillance programme so that these risks may be known earlier. The decision as to how many patients should be treated before allowing a drug on to the market will depend on several factors. A relatively small number may be required for a new drug for a rare fatal disease for which

there is no treatment, but several thousands may be required for a drug which needs to be taken on a long-term basis for a common chronic disease which is rarely fatal and for which there are already acceptable treatments. The regulatory authority will be influenced by the Government who in their turn will be influenced by the general opinion within Parliament which should reflect public opinion.

There have been several occasions when the reaction to the publication of an ADR has resulted in the unjustified condemnation of a medication.

Oxygen and Retrolental Fibroplasia

The discovery in 1953 that 100% oxygen, when given to neonates, could cause retrolental fibroplasia, produced a change in practice which caused a large number of neonatal deaths from hypoxia. Cross and Bolton[20,21] suggested that there were about 200,000 deaths in England and Wales and over 180,000 deaths in the United States over the subsequent two decades. These numbers were sixteen times larger than the estimated number of babies who would have been blinded by a more liberal oxygen policy.

Pertussis Vaccine and Encephalopathy

The reports of neurological illness following the use of pertussis vaccine resulted in the immunisation figures for the UK dropping from 80% of neonates to 31%[22], and produced the largest epidemic of pertussis for 20 years[23]; 3.5% of children in the encephalopathy study had had triple vaccine within 7 days, compared with 1.7% of controls. The relative risk was 2.4; if the child had previously been neurologically normal, the relative risk was 3.3, but there was no significant risk if the child had diphtheria and tetanus vaccine alone. The risk of serious impairment within 7 days was 1 in 110,000 and the risk of permanent impairment was 1 in 310,000[24].

Teratogenicity of Debendox

There remain some controversies concerning ADR where publicity has not helped to resolve the problem. Although on three occasions the Committee on Safety of Medicines has carefully examined all the available data on the issue of whether Debendox for the treatment of morning sickness in pregnancy has produced an increased incidence of congenital abnormalities in the offspring of mothers treated with the

drug, the Committee found no evidence that there was an increased risk of foetal damage with the use of this agent[25]. The adverse publicity attached to this drug produced such a large fall in sales that it was no longer viable commercially and has been withdrawn from the market. It is the first drug victim of trial by the media.

The Risks that we are Prepared to Take

It is very difficult to find out what risks the general public would be prepared to run for an effective drug but one can study the risks they are prepared to take in everyday life and with certain common social drugs (see Table 3).

If we examine the action that various risks have provoked, we will have an idea as to whether the public considers them acceptable or not.

1. Fatal accidents presenting risks of 1:1,000/person/year are infrequent. That immediate action is taken to reduce such hazards suggests that this level of risk is socially unacceptable.
2. At lethal accident levels of 1:10,000/person/year public money is spent to control their causes.
3. Mortality risks of 1:100,000/person/year are still considered candidates for some action.
4. Fatal accidents with a probability of 1:1,000,000/person/year are not of concern to most people.

These figures show the boundaries of acceptable risk to lie between 1:1,000,000 (those associated with natural hazards) and 1:1,000, i.e. the annual per capita illness and disease risks. Society appears to accept voluntary risks with orders of magnitude greater than involuntary risks[26] (see Tables 3 and 4).

Dinman[27] points out that a country (the United States) that accepts 200,000 excess deaths a year associated with smoking and 20,000 excess deaths from not buckling seat belts will not — and to be consistent — should not pursue extreme risks posed by environmental contaminants. More recently, there was considerable opposition to the parliamentary bill which made the fastening of front seat belts mandatory, a move which the BMA had suggested would save more than 700 lives per annum and 11,000 seriously injured per annum[28].

If the subject is of interest I recommend reading *Risk Watch — The Odds of Life* by J. Urquhart and K. Heilmann, Publishers Facts on File Publications, New York and Bicester, England, or in the original German *Keine Angst vor der Angst* published in 1983 by Kindler Verlag, Munich. They suggest the use of safety degree units, which is the number of noughts on the unicohort size, i.e. 5 = 1 in 100,000. They also give the

Table 3 **The risks of common voluntary activities**

Voluntary risks[26,27,28,29]		Death/person/year (odds)
Smoking (20 cigarettes per day)	1 in	200
Drinking (1 bottle of wine per day)	1 in	13,300
Soccer*	1 in	25,000
Car racing	1 in	10,000
Car driving* (UK)	1 in	5,900
Motorcycling (see footnote)	1 in	50
Rock climbing**	1 in	7,150
Taking contraceptive pills	1 in	50,000
Power boating	1 in	5,900
Canoeing	1 in	100,000
Horse-racing*	1 in	740
Amateur boxing*	1 in	2,000,000
Professional boxing**	1 in	14,300
Ski-ing	1 in	1,430,000
Pregnancy (UK)	1 in	4,380
Abortion (legal less than 12 weeks)***	1 in	50,000
Abortion (legal more than 14 weeks)***	1 in	5,900

* Based upon deaths/per million participants/year
** Based upon deaths/per million hours/year spent in sport
*** Based upon deaths/per million pregnancies per year
A figure of 1 death per 1056 registered motorcycles is quoted by Urquhart and Heilmann in *Risk Watch*.