SIDE EFFECTS OF DRUGS ANNUAL 6

A worldwide yearly survey of new data and trends

EDITOR:

M.N.G. DUKES

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How to use this book

THE SCOPE OF THE 'ANNUAL'

Side Effects of Drugs Annual has been published in January of each year since 1977. It is designed to provide a critical and up-to-date account of new information relating to adverse drug reactions and interactions from the clinician's point of view. The Annual can be used independently or as a supplement to the standard encyclopedic work in this field, *Meyler's Side Effects of Drugs*, the ninth edition of which was published in March 1980.

℞ SPECIAL REVIEWS

As new data appear, older findings may be discredited and existing concepts may require revision. More than fifty 'special reviews' deal critically with such topics, interpreting conflicting evidence and providing the reader with clear guidance. Special reviews are identified by the traditional prescription symbol and are printed in italic type. Older papers cited in these reviews are either listed by name or via cross references to previous Annuals or past editions of Meyler's Side Effects of Drugs, which can be found in most medical libraries.

SELECTION OF MATERIAL

In compiling the SED Annual particular attention is devoted to those publications which provide essentially new information or throw a new light on problems already recognized. In addition, some authoritative new reviews are listed. Publications which do not meet these criteria are omitted. Readers anxious to trace all references on a particular topic, including those which duplicate earlier work, are advised to consult *Adverse Reactions Titles*, a monthly bibliography of titles from approximately 3400 biomedical journals published throughout the world, compiled by the international Excerpta Medica abstracting service.

PERIOD COVERED

The present Annual reviews all reports presenting significant new information on adverse reactions to drugs from August 1st 1980 up to July 31st 1981. Where possible more recent papers have been included. Subsequent Annuals will cover the world literature appearing yearly between August 1st of one year and July 31st of the next.

CLASSIFICATION

Drugs are classified according to their main field of application or the properties for which they are most generally recognized. In borderline cases, however, some supplementary discussion has been included in other chapters relating to secondary fields of application. Fixed combinations of drugs are dealt with according to their most characteristic component.

DRUG NAMES

Drug products are in general dealt with in the text under their most usual non-proprietary names; where these are not available, chemical names have been used; fixed combinations usually have no non-proprietary connotation and here trade names have been used as necessary.

SYSTEM OF REFERENCES

References in the text are coded as follows:

R: In the original paper, the point is *reviewed* in some detail with reference to other literature.

r: The original paper *refers* only briefly to the point, on the basis of evidence adduced by other writers.

C: The original paper presents detailed *original clinical evidence* on this point.

c: The original paper provides *clinical evidence*, but only briefly.

The code has not been applied to animal pharmacological papers. The various Editions of *Meyler's Side Effects of Drugs* are cited in the text as SED 8, SED 9, etc.; *SED Annuals 1–5* are cited as SEDA-1, SEDA-2, etc.

INDEXES

Cumulation: To facilitate rapid searching, the indexes to the SED Annuals are cumulative over periods of approximately 4 years. The indexes in the present Annual have been cumulated with those of Annuals 4 and 5.

Index of Drugs: This index provides a complete listing of all references to a drug in Annuals 4, 5 and 6.

Index of Side Effects: This index is necessarily selective, since a particular side effect may be caused by very large numbers of compounds; the index is therefore mainly directed to those side effects which are acute or life-threatening or are discussed in special detail in Annuals 4, 5 and 6. Before assuming that a given drug does not have a particular side effect one should consult the relevant chapter as well as the indexes in SEDA-3 and SED 9.

Index of Interactions: This index lists all major interactions discussed in Annuals 4, 5 and 6.

The indexes have been compiled by Dr H. Kettner, Middelburg, The Netherlands.

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SIDE EFFECTS OF DRUGS ESSAY 1982*

Science vs practice and/or practice vs science?

István Bayer

The Health of Mankind is in large measure dependent upon the Health of Medicine. The Health of Medicine in turn depends on the relationship between medical sciences and medical practice. Ideally, this relationship should assure a highly efficient practical exploitation of research results; in fact it does not always do so. Drug therapy constitutes a good example of the difficulties associated with this process.

In theory, the flow of scientific data selected by the pharmaceutical industry to the practitioner (under the watchful eye of the regulatory agencies) should serve 2 purposes at the same time: Firstly, the practitioner should in this way be sure of obtaining all the information which he needs if he is to use drugs as effectively and safely as is humanly possible. Secondly, the guarantee should exist that this objective and factual information will not be biased or discredited by reckless intermixture with a flow of subjective narrative, unevaluated 'data', or purely commercial information. The practitioner's role in this process appears at first sight to be purely passive, since he is at the receiving end of the information chain. In fact, the situation is not so simple.

There are 2 separate (but always overlapping) phases in the life of a drug on the market. Just after its introduction the events which surround it can be compared with the transfer of the drug's manufacture from the laboratory or pilot unit into the large-scale production plant. Later, as the use of the drug becomes accepted in a much wider circle, events more closely resemble the transfer of established technology to a new manufacturer. Particularly during the earliest phases in the life of a drug, stringently planned clinical pharmacological research will explore and detect new therapeutic possibilities beyond the strict limits of the original licence, adding here and there a caveat based either on new facts or new uncertainties. Practitioners are too little aware of the fact that during this first period they are necessarily participants in the continuing therapeutic research process and thus contributors to the evaluation of the efficacy and safety of a new therapeutic agent. Detection of side effects and adverse drug reactions constitutes a vital element in their activities. Hence this field could be a model for a symbiosis and a beneficial interaction between research and practice in which the practitioner is an active 'donor', and not merely a 'recipient'.

It is the undisputed moral obligation of the manufacturer to ensure that the positive and negative aspects of the therapeutic use of his product be equally and objectively investigated by up-to-date scientific methods. Beyond this accepted moral obligation, however, a series of legally binding duties have progressively come into existence, as drug regulatory agencies have come into being and have been accorded responsibility for the establishment of evidence as to the efficacy and relative safety of drugs which they authorize. In the greater part of

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* The side effects of drugs essay is written each year by guest authors. Dr. Bayer is Director of the National Institute of Pharmacy and Professor of Pharmacy at the Postgraduate Medical School, Budapest, Hungary.

the world, the responsibility for drug evaluation and benefit/risk decisions lies today with these agencies.*

Since it is impossible to evaluate anything but truly scientific data and results, the performance of experiments and trials, the drawing of conclusions and the presentation of results on any matter relating to a drug must be in conformity with the rules of science, including its mathematic and statistical requirements. In this light it is much easier (at least in theory) to produce scientific evidence on the efficacy of a new drug than on its side effects or the harmful consequences of its use. Preclinical animal testing and Phase I and II experiments in man provide a series of prophecies and expectations on the basis of which a systematic and sharply focused qualitative evaluation of the expected therapeutic efficacy of a new drug can be undertaken in Phase III. For a systematic detection and study of expected side effects and other adverse reactions the relevant information provided by preclinical toxicity studies is generally much more meagre. This is inevitable, for (quite apart from the relatively poor correlation between species where adverse effects are concerned) those drugs which are proven in animal tests to be 'too toxic' for experimentation in humans are discarded in that phase and never reach the clinician. Consequently, clinical pharmacologists and clinicians have at the outset very limited information that can be used as a starting point for the systematic detection and analysis of side effects. In addition, in contrast with the high 'incidence rate' of the desired effect (which ideally can be observed and measured in every case) side effects are likely to manifest themselves only occasionally. The danger will always persist that, even in the case of the most carefully investigated and scientifically evaluated drug, a side effect will remain undetected for a long period if it does not chance to appear in the relatively limited population involved in clinical pharmacological research and clinical investigations. The existence or the non-existence of side effects, however, influences directly the decision as to the benefit/risk ratio; consequently, if a severe side effect is discovered after approval, the drug must be re-evaluated and the benefit/risk assessment revised. It is thus a fact of a drug's life that significant data can be expected to emerge (and must be collected) in Phase IV, but there is a great diversity of opinions concerning the ways and means to be followed to this end.

Monitored release techniques can fairly be regarded as the most efficient of all the methods available so far; a maximum of data and information can be obtained by collecting experiences and observations from every physician prescribing the drug. The large number of reports obtained permits statistical analysis and scientific evaluation; it is then possible to undertake studies in depth for the clarification of the specific suspicions which may emerge, and to go back, if necessary, to the pharmacological or toxicological experiment and investigate the causes and course of a toxic or obscure reaction in animal models. The use of monitored release techniques can for such reasons be considered the ideal approach to the detection of side effects; unfortunately it is impossible to apply them to every new drug, since they impose a heavy burden on practitioners and upon the monitor, and their over-frequent use would transform a scientific activity into a routine which would probably be carried out with everlessening interest and completeness. These are the reasons why most countries still have to rely mainly upon their spontaneous drug monitoring systems, employing monitored release only exceptionally or not at all.

Our experience with spontaneous reporting of adverse drug reactions in Hungary is largely identical to that of other countries, including the disappointment of enthusiastic people, who had expected thousands of reports, when they came to realize that the number of reports submitted was in fact very small and the overwhelming majority of them unfit for evaluation. It would be unfair to declare that this failure is the fault of practitioners only; the fact that a side effect reported by him is already well-known can easily be overlooked by a practitioner; and he may be entirely unaware of the extent to which his patient has succeeded in collecting prescriptions from other physicians or in supplementing his medication with over-the-counter drugs or even prescription drugs from his own household stock, thus entirely confusing the adverse reaction issue. Nevertheless, in Hungary, as in other countries,

* The term *responsibility* does not imply that practical evaluation should be performed by the agencies themselves.

practitioner reports have led to the detailed re-investigation of several drugs and the suspicions raised were proven to be well-founded in more than one instance.

The time of 'Great Expectations' following the introduction of national drug monitoring systems is over; we are now in a position to look at national and international drug monitoring systems objectively, without under- or overestimating their value. The situation was very clearly formulated by Dr. Kimbel in 1978 when he wrote that 'National Drug Monitoring Systems are almost all of the spontaneous type and serve to generate signals rather than to supply quantitative data' (Kimbel, 1978), but generating signals is a very meritorious activity, even if it is not an end in itself.

Practitioners therefore can and should be reminded that their reports are essential for drug evaluation and safety. They should report immediately to the national center every observation which could be of importance; they should not be afraid to send reports on the effects of incidental overdoses. Reports can also be sent to the manufacturer, but it is essential that the observations in question be reported simultaneously to the national center as well. It would be unfair to suppose that most manufacturers would seek to conceal these reports from the health authorities, but there are indeed cases where a manufacturer, who is convinced that he has a complete picture of his own product, simply does not believe a report and does not consider it necessary to transmit this information to the national center. It is also a fact that in some countries manufacturers are afraid of the over-reaction on the part of the authorities, sometimes justifiably so. At the same time, practitioners should never be in a hurry to publish a paper or to write a letter to the editor of a periodical before consultation with the national center. Practitioners should be aware that side effects and adverse reactions need to be evaluated in the same scientific manner as therapeutic effects and the publication of unevaluated data may improperly discredit a drug; there is certainly no harm in voicing a suspicion, but the average practitioner is not always in a position to decide independently when and how this can best be done so as to alert without alarming.

Consultation with the national center supposes, of course, the existence of an active national center, which is prepared both to act and to cooperate closely with the reporting practitioner. The national center should also cooperate with the manufacturer. There are at least 2 reasons for this cooperation: Firstly, the manufacturer is really the one who knows his own product best; consequently, he is in a position to provide the national center with relevant supplementary information and it is the manufacturer's primary interest that his product should not produce harm. Most manufacturers therefore will cooperate in the clarification of doubts and in the addition of warnings to the text of package inserts or other materials. If the national center starts hiding reports from manufacturers, the latter will follow this bad example in non-communication and the final result is a game of hide-and-seek in which drug safety will be the only loser.

National drug monitoring systems should thus be based on cooperation between practitioners, manufacturers, national centers, experts in clinical pharmacology and regulatory agencies. Once such cooperation has been established, the practitioner's individual report and indeed the entire system can be used for several purposes. The range of possibilities offered by the existence of a national drug monitoring system deserves to be reviewed here briefly.

In Hungary, where our Institute (which functions as the national drug regulatory agency) is in charge of the management of the drug monitoring center, we have introduced a simple checking system: every report on adverse drug reactions is considered as a *potential drug defect report*; consequently, a pharmaceutical quality check on the preparation (including the excipients) is the first step to be taken. Up to now we have not in fact identified cases in which quality defects were responsible for an adverse reaction, but we maintain this check *firstly* in order to avoid superfluous clinical pharmacological research, and *secondly* to ensure the manufacturer's compliance with the registered standard of this product. This check is a prerequisite before processing the report to the competent clinical pharmacologist and to the manufacturer. If there is reason to suspect that the drug was not properly used, another check is undertaken: the adequacy of the information on the use of the drug (i.e. the text on the package insert and other written information issued on the drug) is re-examined in the light of the report.

These are only 2 examples of the multiple use which can be made of practitioners' re-

ports, but there are other possibilities as well if we consider drug monitoring as an integral part of postmarketing surveillance.

In this context I should like to quote Lasagna, who has pointed to a number of questions connected with postmarketing surveillance (Lasagna, 1980):

'There is therefore good reason for surveying the use of drugs in the postmarketing state, but not only to detect previously unsuspected toxicity. Rather, we should be interested in such questions as the following:

- Are physicians using the drug for the accepted indications? If not, why not?
- Is the drug performing about as expected?
- Is the adverse reaction profile, qualitatively and quantitatively, what was predicted on the basis of premarketing experience?
- Are new adverse effects being observed?
- Is the drug being over- or underprescribed?
- Is abuse of the drug by patients a problem?
- What is the clinical picture in cases of gross overdosage? What therapeutic measures are required in such cases?
- How are the drug's effects modified by hepatic or by renal disease?
- What drug-drug interactions are important?
- Are there age-related differences in response to the drug? What dosage do infants and small children require, and what the elderly?
- Is the drug safe when taken by pregnant women?
- Have new uses for the drug come to light?'

Each question is directly related to the quality of drug therapy, but these questions must well be divided into 2 classes: those belonging to the drug evaluation process (on the assumption that Phase IV is an integral part of that process), and those intended for the study of compliance.

Compliance assurance in the broadest sense is indeed one of the most important tasks which can be accorded to well-constituted drug control agencies, and it is very important that compliance assurance programs should cover the entire field. This comprises: the compliance of the manufacturer with the master file, regulations on Good Manufacturing Practice, recognized quality standards and other registration norms; the compliance of manufacturers, drug distributors and professional organizations with regulations designed to ensure the provision of objective and unbiased information on drugs; the compliance of the distribution network with general and individual requirements (for example: the maintenance of proper storage conditions); the compliance of the prescriber with the indications and conditions of use recommended by the manufacturer and/or drug regulatory bodies or at least those well founded in the literature; and last but not least the compliance of the patient with the therapeutic regimen which has been prescribed for him.

Dr. Lasagna is right when he suggests that answers to his questions should be sought in the postmarketing phase, because, and I shall quote him again:

'We shall have to study drugs in what I have called the 'naturalistic' setting, i.e. as they are actually prescribed by physicians and taken by patients, with all the vagaries and errors and the potential for abuse that exist in this setting' (Lasagna, 1979).

If drugs were evaluated in the light of experience in this 'naturalistic' setting, Phase IV of the drug introduction process and the quality of drug therapy could be greatly improved and there would be no risk of finding medical science and medical practice in the position of the 2 faces of Janus, which never see each other.

REFERENCES

Kimbel, K. H. (1978): Drug monitoring, why care? In: *Side Effects of Drugs Annual 3*, p. ix.

Lasagna, L. (1979): Wanted and unwanted drug effects: the need for perspective. In: *Side Effects of Drugs Annual 4*, p. vi.

Lasagna, L. (1980): Postmarketing surveillance. *Triangle, 19/3*, 108.

Contents

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1 Central nervous system stimulants and anorectic agents

CNS STIMULANTS

Theophylline and aminophylline *(SED 9, 3)*

Theophylline and fatal asthma During the compilation of the present volume a controversy arose in the pages of *The Lancet* as to the possible involvement of oral theophylline in an increased incidence of asthma deaths in various countries. The discussion was opened by a paper from New Zealand in which Wilson et al. (1[C]) pointed on the one hand to evidence for an increased incidence of asthma fatalities and on the other to the 'increasing use of theophylline, particularly sustained preparations', the hypothesis being advanced that there was a causal relationship. The increase in deaths had apparently primarily involved young people, and the authors suggested an additive toxicity between oral theophylline drugs and inhaled β-agonists, causing cardiac arrest.

The validity of the data has been strongly challenged by various groups: Beaglehole et al. (2[r]), also from New Zealand, have questioned both the correctness of the view that asthma deaths have increased and the fact that prescribing habits have changed towards a greater use of theophylline.

Although the debate will no doubt continue, it has elicited several important pieces of ancillary evidence on this type of patient. Toennesen (3[c]), from Denmark, has for example shown how many users of asthma remedies, including theophylline, admit to increasing their dosage above the prescribed level when their condition deteriorates. Koeter et al. (4[c]) from The Netherlands have found some recent cases of deaths in young asthmatics to have been due to use or overuse of β-sympathomimetic agents alone, a fact which recalls an epidemic of deaths from this cause some years ago (See Chapter 14).

Dose-dependent reactions In a study by Ramsay et al. (5[CR]) a series of consecutive medical inpatients expected to benefit from a theophyllinate were treated with sustained-release aminophylline in a protocol conforming with ordinary practice. Five of 16 patients were adjudged toxic during treatment with aminophylline 450 mg daily, all with vomiting. The side effects were transient in 2 patients, but returned in more severe form when the dose was increased to 900 mg daily. A further 3 patients suffered toxicity at the 900 mg dose, 2 with vomiting and the third with a confusional state. Vomiting was accompanied by nausea and malaise, and was not related to tablet ingestion. Two patients had hematemesis. One patient developed a severe confusional state when the dose was increased to 900 mg daily, and recovered about 24 hours after the drug was discontinued. Toxicity was significantly less common in cigarette smokers (see SEDA-5, 1) and was related to higher plasma theophylline concentrations. However, there was a large overlap between the concentrations associated with toxicity (as low as 9 μg/ml) and the accepted therapeutic range (5–20 μg/ml). Most patients with toxicity had theophylline levels within the therapeutic range. There was a 7-fold variation between patients as regards plasma theophylline, with higher concentrations in non-smokers, infrequent alcohol users, older patients, those with left ventricular failure and those with lower serum transaminases. The authors considered that these variables could not be separated completely because of the small number of observations.