

Jerzy BRANDYS

Drug therapy: safety, effectiveness, and economics

Farmakoterapia: bezpieczeństwo, skuteczność, ekonomia

Department of Toxicology
Faculty of Pharmacy
Medical College
Jagiellonian University, Kraków
Head: Prof. dr Jerzy Brandys

Additional key words:

pharmacovigilance
pharmacoeconomics
internet

Dodatkowe słowa kluczowe:

monitorowanie skutków
farmakoekonomika
internet

The problems of safety, effectiveness and economics of a drug therapy are discussed. Adverse drug reactions (ADR) represent not only a humanistic problem but also an epidemiological and economic one. The incidents and costs of ADRs are described, as well as pharmacovigilance and pharmacoeconomics as a tool of rationalizing the expenditures on health care.

The development of a pharmaceuticals is a stepwise process involving an evaluation of both the animal and human safety information. The goals of the non-clinical safety evaluation include: a characterization of toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility. The non-clinical safety studies should be adequate to characterize potential toxic effects under the conditions of the supported clinical trial. Other non-clinical studies include pharmacology studies for safety assessment (safety pharmacology) and pharmacokinetic (ADME) studies. Safety pharmacology includes the assessment of effects on vital functions, such as cardiovascular, central nervous and respiratory systems, and these should be evaluated prior to human exposure. The non-clinical safety study recommendations for the marketing approval of a pharmaceutical usually include single and repeated dose toxicity studies, reproduction toxicity studies, genotoxicity studies, local tolerance studies and for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential. Exposure data in animals should be evaluated prior to human clinical trials. Further information on absorption, distribution, metabolism and excretion animals should be made available to compare human and animal metabolic pathways.

This preclinical phase, if satisfactory completed, is followed by a clinical research divided into three phases. The aims of the **first phase** is to study pharmacodynamics and pharmacokinetics in generally healthy volunteers although, for some categories, cancer chemotherapeutic agents it is necessary to undertake these studies in patients with the particular disease. **Phase 2** aims at investigating the therapeutic potential of the new drug in relatively small patient population, often around 200 to 500. It will usually be undertaken as one or more random-

W publikacji omówiono problem skuteczności, bezpieczeństwa i racjonalności ekonomicznej farmakoterapii. Niepożądane działania leków stanowią nie tylko problem humanistyczny ale i epidemiologiczny i ekonomiczny. Opisano częstość oraz koszty działań niepożądanych. Ponadto metodę monitorowania skutków działania leków (pharmacovigilance) oraz farmakoekonomiki jako narzędzi w racjonalizowaniu wydatków na opiekę zdrowotną.

ized controlled trials, studying different doses, and seeking preliminary evidence of both clinical efficacy and safety. **Phase 3** is concerned with a more rigorous examination of the drugs efficacy and safety, as randomized controlled trials, in patient populations that can vary in size from a few hundred to several thousands [4].

Despite the complexity of the process of new drug development, relatively little will be known about its effects under normal conditions of use, after marketing, because the circumstances of clinical practice differ so markedly from those of clinical trials. The limitations to premarketing studies are several.

Number of patients: clinical trials are performed in limited numbers of patients, and the average that is exposed to a new drug when it is first marketed is around 1 500. This precludes identifying adverse drug reactions (ADR) with an incidence of less than 1:100 to 1:500. Nevertheless, once marketed a new drug may be taken by millions of people, and rare adverse effects may appear which have not previously been identified.

Length of exposure: clinical trials are generally of relatively limited duration and for many drugs, are much shorter than the expected length of treatment in normal clinical practice.

Representativeness of target population. Phase 1 and phase 2 studies are usually performed in healthy volunteers and patients, who may not be representative of the future populations susceptibility to ADRs. Phase 3 clinical trials are also performed in highly selected patients. The very young and the frail elderly are generally excluded whilst women and certain ethnic minorities are underrepresented. The severely ill and those with co-morbidity also tend to be excluded. By contrast, patients in clinical trials usually have more precise and clear cut diagnoses than patients those in routine practice.

Adres do korespondencji:
Prof. dr hab. Jerzy Brandys
Katedra i Zakład Toksykologii CM UJ
ul. Medyczna 9
30-688 Kraków, Poland
tel/fax: 12 658 82 14
e-mail: mbrandys@cyf-kr.edu.pl

Drug interactions. The treatment of participants in clinical trials is generally limited to the drug under study together with a small range of other products thus precluding the identification of unanticipated drug-drug-interactions.

Clinical evaluation. In clinical trial the evaluation of efficacy and safety is based on predefined end-points and, in general, patient follow up is more frequent and comprehensive than in routine clinical practice when clinical circumstances may dictate a rather different style of practice depending on both the prescriber and the patient.

These limits to the extent with which the safety profile of a new drug can be defined before marketing are inevitable. They emphasize the fact that, whilst the quality and efficacy of a new drug can be clearly established before marketing authorization, any assessment of safety must necessarily be provisional. It is therefore essential that potential ADRs of new drugs are carefully scrutinized during routine use.

Adverse drug reactions are harmful effects of drugs occurring during normal conditions of use.

Type A reactions can usually be predicted from its known pharmacological or toxicological properties. They are typically dose-dependent, relatively frequent, and benign in nature. Examples include hypotension with antihypertensive agents, dry mouth and blurred vision with tricyclic antidepressants, and dyspepsia with non-steroidal anti-inflammatory drugs. They may, nevertheless, encompass serious ADRs such as haemorrhage with thrombolytics or blood dyscrasia with cytotoxic anticancer drugs.

Type B reactions are qualitatively abnormal drug effects unrelated to a particular drug's pharmacological properties. They are usually unpredictable from preclinical studies, and are rarely dose-dependent.

Drug therapy is therefore a balance between safety and efficacy or risk and benefit. Main factors which influence the occurrence of ADRs are following: multiple drug therapy, age, multiple disease states and types of drugs prescribed e.g. [7].

The risk of ADRs increases when a patient is hospitalized, owing to the high number of drugs prescribed per patient at any one time. Approximately 10-20% of hospitalized patients are thought to have experienced an ADR during their hospital stay and, 5% of all hospital admissions are due to ADRs, although estimates of drug-related admissions range from 3% to 27% depending on the patient population studied. Up to 3% of deaths in hospital inpatients are to be due to the adverse effects of drugs.

Estimates of the incidence of ADRs in general practice vary widely, from 2% to over 44% depending on the study methodology. In Australia an incidence of between 2.4% and 3.5% was found and in USA an incidence of between 3.1% and 6.2% was found. The mortality found in the study in French teaching hospitals was very similar (ca. 0.13%) to that found in United States [13]. Admissions caused by adverse reactions are only one aspect of drug related morbidity and account for about 10% of the

adverse effects observed in probably occurs in the community and never leads to admission hospitals. A large proportion of these ADRs are considered to be preventable through good prescribing practice, mainly by individualizing dosage, and avoiding inappropriate and unnecessary drug therapy.

To assess the true incidence of the problem in the community more studies are required. This represents a significant cost to the society (e.g., National Health Service) in terms of bed occupancy and treatment of these adverse effects.

A contributing factor in preventable hospital admissions and associated direct costs and, of course, exerting a significant negative impact on healthcare outcomes is a phenomenon of noncompliance [11]. It has been long recognized that patients do not follow instructions for use of their medication routinely. The estimations of the percentages of patients who does not adhere to their instructions vary in different studies from 20% to 82%. It tends to increase with the number of medications taken and the complexity of the regimen. Electronic monitoring has demonstrated an improvement from 59% compliance with a 3 times daily regimen to 83.6% for a once daily prescription [11].

Another factor of ADRs is inappropriate prescribing for elderly patients and has become a concern from both humanistic and economic viewpoints. Prescribing medications for the elderly involves an understanding of age-related changes in the structure and function of various organ systems that may alter the pharmacokinetics and pharmacodynamics of many drugs. Inappropriate use of prescription medications can have severe clinical consequences in the elderly. Studies suggest that geriatric patients are at high risk for complications due to inappropriate prescribing and that such complications may be manifested as serious drug-related morbidity or mortality [5].

A discipline concerned with identifying and responding to safety issues, with marketed medicines is **pharmacovigilance** [8]. Its aims are:

- identifying previously undescribed ADRs to particular drugs, estimating their incidence, end elucidating predisposing factors,
- identifying increases in the incidence of known ADRs to particular drugs, and elucidating the causes,
- communicating ADRs issues to prescribers, manufacturers and consumers, and
- proposing public health measures in order to less the burden of iatrogenic disease.

Detecting signals of possible hazard remains the most difficult aspect of pharmacovigilance. Predicting or detecting risk at an early stage is generally less of a problem with type A reactions, which are related to the pharmacological properties of a drug and may therefore be anticipated. However, type B reactions, which are, by definition, unrelated to the known pharmacological activity of the drug and therefore unpredictable, still have a remarkable capacity to surprise de-

spite the great increase in awareness in recent years. Systems of pharmacovigilance have improved immeasurably since the events of thalidomide or the oculo-mucocutaneous reaction to practolol, but we should not imagine that similar problems would not occur in the future. For an example of the continuing frailty of pharmacovigilance systems, consider the persistent dry cough which commonly complicates angiotensin converting enzyme (ACE) inhibitor treatment. The adverse reaction escaped detection through the entire pre-registration program, (considered capable of detecting reactions occurring at a frequency of one in 100), and even after marketing-yet it occurs in no less than 15% of all patients.

The detection of rare adverse events still depends heavily upon voluntary reporting schemes or registers [9]. Advances in computer methods may have improved the handling and review of voluntary reports and have enabled also the sharing of data between national registries. Assessment of the data for signals of potential hazard remains the most taxing step in these systems, however methods of generating signals from voluntary reporting systems do not appear to be uniform. Some depend largely upon intuitive assessment by physician with knowledge and experience of adverse reactions. Others [3] employ formal methods such as algorithms to assess the likelihood of causality. Reports of single cases or small series of putative adverse reactions have proved remarkable successful in providing early warnings of major drug hazards.

The rapid growth of healthcare expenditures, coupled with a deceleration in the growth of the general economy, has led to increased interest in economic evaluations of healthcare programmes, and especially for drugs [15,16]. **Pharmacoeconomics** has been defined as "the description and analysis of the costs of drug therapy to health care systems and society" [10]. pharmacoeconomics research identifies, measures, and compares the costs and consequences of pharmaceutical products and services [1].

The validity of pharmacoeconomics studies mainly rely on three major dimensions in terms of methodology: strategy, cost valuation, study design. There are 4 main types of pharmacoeconomics analysis. The **cost-minimization analysis** (CMA) is used when two or more interventions are examined and demonstrated or assumed to be equivalent in terms of a given outcome or consequence. Costs associated with each intervention may be examined and compared. The **cost-effectiveness analysis** (CEA) is the most commonly used economic evaluation. It compares the outcomes in terms of their monetary cost per unit of health outcome, e.g., cost per case prevented, cost per life saved, or cost per year of life saved. CEA is the most appropriate analysis design when the goal of the analysis is to identify the most cost-effective prevention strategy from among a set of options that produce a common outcome. The **cost-utility analysis** (CUA) compares the outcome of decision options in terms of the

subjective value or preferences of individuals or society for outcomes, e.g., quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs). This analysis considers not only the number of cases prevented but also the length of life and its quality. For example, a program that produces a longevity of 20 years during which people function at only one-half of what they consider to be full health would be equivalent to a program that produces a longevity of 10 years during which people function with full health. The **cost-benefit analysis** (CBA) compares the outcome of decision options in terms of monetary units. Therefore, both costs and outcomes are measured on monetary terms. In CBA, all costs and benefits are valued, e.g., value of lost wages due to disability (an example of indirect costs) and value of pain (an example of intangible costs). As a result, this analysis becomes quite complex and difficult to perform [10,12].

Cost valuation represents one of the main difficulties in pharmacoeconomics studies. Different type of costs must be taken into account. Direct costs are represented by the sum of expenditure involved in the consumption of medical and non medical products or services. Direct costs usually include hospital cost, physician fees, cost of drugs and etc. Non medical direct costs are expenses made by the patient or his family that are directly related to treatment such as food, accommodation or travel expenses. Indirect costs are those that occur because of loss of health and productivity and may result from morbidity or mortality. Intangible costs represent another category of costs and are difficult to measure. These are the costs of pain, suffering grief and other non financial outcomes of disease and medical care.

Recently a new term "outcomes research" is becoming more used. It means the application of methods for evaluating relative patient and social benefits in terms of therapeutic and economic effectiveness and quality of life. Three levels of health care evaluation are concerned: **efficacy**-single clinical outcome, **effectiveness**-global clinical

outcome and therapeutic benefit and **efficiency**-outcome versus cost [12,14].

The health care costs of drug-related problems represents a serious economic problem. Medications are prescribed for the treatment of disease with the intent of achieving an optimal therapeutic outcome. In the past, optimal therapeutic outcome has been defined as the "the right drug, for the right patient, at the right time" [7]. More recently, optimal therapeutic outcome implies the absence of drug-related problems (DRPs). Unresolved and/or unrecognised DRPs may manifest as drug-related morbidity and may eventually lead to drug-related mortality. There is considerable evidence that a large proportion of drug morbidity is preventable. Recent studies indicate that the substantial costs associated with inappropriate drug use are likely to exceed the initial outlays for drug therapy [6].

Use of the **Internet** is becoming widespread throughout the world [2]. Its use in the domain of drug safety and pharmacovigilance is spreading rapidly. The Internet has already begun to have an impact on the way drug safety and pharmacovigilance are being carried out. The impact has not been felt directly but rather as fallout from areas that are using the Internet heavily such as advertisers and groups establishing chat rooms or discussion forums. In addition, various governmental groups are beginning to define the requirements for electronic data transmission, initially using physical media (e.g. CD-ROMs, diskettes) but eventually by using direct Internet or internet-compatible electronic transmission. The impact of the Internet is expected to be felt in the next 2 to 5 years in all areas touching drug safety.

Drug therapy is a balance between safety and efficacy or risk and benefit. The factor which determine the favourability or otherwise risk to benefit ratio include both the seriousness of the underlying disease, the effectiveness of the drug in its treatment, and the nature and seriousness of the drug's ADR profile. Reliable assessment of pharmaceutical benefits and risks – and their economic consequences are essential for

drug developments and public health.

References

1. **Clemens K., Townsend R., Luscombe F. et al.:** Methodological and Conduct Principles for Pharmacoeconomic Research. *PharmcoEconomics* 1995, 8, 169.
2. **Cobert B., Silvey J.:** The Internet and Drug Safety. *Drug Safety* 1999, 20, 95.
3. **George Ch. F.:** Predicting adverse drug reactions. In: Nimmo W.S. Tucker G.T. (Eds). *Clinical measurement in drug evaluation*. John Wiley&Sons Ltd. Chichester, New York 1995, 291.
4. **Jackson P. R., Wallis E.J., Yeo W.W., Ramsay L.E.:** What number of patients is necessary to establish drug safety?. In: Nimmo W.S. Tucker G.T. (Eds). *Clinical measurement in drug evaluation*. John Wiley & Sons Ltd. Chichester, New York 1995, 245.
5. **Johnson J.A., Bootman J.L.:** Drug-related morbidity and mortality. A cost-of-illness Model. *Arch. Intern. Med.* 1949, 1995, 155.
6. **Johnson J.A., Bootman J.L.:** Drug-related morbidity and mortality and the economic impact of pharmaceutical care. *Am. J. Health-Syst. Pharm.* 1997, 54, 554.
7. **Langman M.J.S.:** Controlled clinical trials: contribution to drug safety. In: Nimmo W.S. Tucker G.T. (Eds). *Clinical measurement in drug evaluation*. John Wiley&Sons Ltd. Chichester, New York 1995, 218.
8. **Laporte J.R., Rawlins M.D.:** Pharmacovigilance. *Pharm. Policy & Law* 1999, 1, 49.
9. **Lawson D.H.:** Accuracy of adverse data from post-marketing studies and the influence on extension of licensed indications. In: Nimmo W.S. Tucker G.T. (Eds). *Clinical measurement in drug evaluation*. John Wiley&Sons Ltd. Chichester, New York 1995, 267.
10. **Malek M.:** Current Principles and Application of Pharmacoeconomics. *PharmacoEconomics* 1996, 9, Suppl.1, 1.
11. **Paes A.H.P., Bakker A., Soe-Agnie C.J.:** Measurement of patient compliance. *Pharm. World Sci.* 1998, 20, 73.
12. **Peys F.:** Pharmacoeconomics: where is the link with pharmacokinetics and biopharmaceutics?. *Pharm. World Sci.* 1997,19, 73.
13. **Pouyanne P., Haramburu F., Imbs J.L., Begaud B.:** Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. *BMJ* 2000, 320, 1036.
14. **Powers-Cramer M., Saks S.R.:** Translating Safety, Efficacy and Compliance into Economic Value for Controlled Release Dosage Forms. *Pharmaco-Economics* 1994, 5, 482.
15. **Schmid G.P.:** Understanding the essentials of economic evaluation. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 1995, 10, Suppl. 4, 6.
16. **Sperry R.J.:** Principles of Economic Analysis. *Anesthesiology* 1997, 86, 1197.

