Post-Marketing Surveillance and Adverse Drug Reactions

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A fundamental axiom in the field of pharmacoepidemiology is that all therapeutic interventions produce unintended drug effects. While there will never be an absolute guarantee of drug safety, it is extremely important to define a drug's safety profile. Although we all encounter disease during our lives, how much more distressing when the disease results from drugs intended to promote health rather than impair it.

Drugs are developed and used to prevent and treat diseases and symptoms, and our continued reliance on them is a testament to their safety and effectiveness. However, one should always bear in mind that agents that have the power to alter biological processes to our benefit can also alter other biological processes to our detriment. To live up to the dictum that, first, we should do no harm (*Primum Non Nocere*), or at least less harm than good, we must use our best evaluative methods to measure drug effects, both beneficial and adverse. Hence, the objective of this article is to review the development and regulation processes of drugs carried out in order to assure their safety throughout their life cycle.

The history of drug regulation

The first act pertaining to the regulation of drugs was enacted in the United States in 1906. This legislation, the Federal Food and Drug Act, dealt with the interstate transport of adulterated or misbranded foods and drugs, and contained no obligations to establish drug efficacy and safety. The federal act was amended in 1938 following the deaths of about 100 children that resulted from the marketing of a solution of sulfanilamide in diethylene glycol, an excellent but highly toxic solvent. The amended act, the enforcement of which was entrusted to the Food and Drug Administration, was concerned primarily with the truthful labeling and safety of drugs. Toxicity studies were required, as well as approval of a new drug application, before a drug could be marketed and distributed. However, no proof of efficacy was required, and drugs could go from the laboratory to clinical testing without approval by the FDA. Since efficacy was not rigorously defined, a number of therapeutic claims could not be supported by data.

The risk-to-benefit ratio was seldom mentioned, but it emerged in a dramatic fashion early in the sixties when thalidomide was introduced in Europe. A short time later it became apparent that the incidence of a relatively rare birth defect, phocomelia, was increasing. It soon reached epidemic proportions, and retrospective epidemiological research firmly established the causative agent to be thalidomide taken early in the course of pregnancy. The thalidomide trauma resulted in changes to the Food, Drug and Cosmetic Act in 1962. Several amendments were made. These mandated: a) sufficient pharmacological and toxicological research in animals before a drug can be tested in humans, b) that the data from such studies be submitted to the FDA in the form of an application for an investigational new drug before clinical studies are carried out, c) proof of efficacy, and d) documentation of relative safety in terms of risk-to-benefit ratio for the disease to be treated [1].

Drug development

By the time an IND[1] is initiated and a drug reaches the stage of testing in human beings, its pharmacokinetic, pharmacodynamic, and toxic properties have already been evaluated *in vitro* and in several species of animals in accordance with current regulations and guidelines.

Trials of drugs in humans are generally conducted in three phases that must be completed before a new drug application can be submitted to the FDA for review [2]. Although assessment of risk is a major objective of such testing, this is far more difficult than the determination of whether the drug is efficacious or not for a selected clinical indication. Usually, about 500 to 3,000 carefully selected patients will receive the new drug during phase III of the clinical trials. At most, only a few hundred are treated for more than 3 to 6 months, regardless of the intended duration of therapy that will be required in common practice. Thus, only the most profound and overt risks that occur soon after administration of the drug can be detected in phase III studies, and only when these occur at a higher probability than 1 per 100 administrations.

Risks that are medically important but delayed, or those with a probability of less than 1 in 1,000 administrations, might not be detected prior to marketing. It is thus obvious that a number of unanticipated adverse and/or beneficial effects of drugs are detectable only after the

[1] IND = investigational new drug

drug is used extensively. Moreover, the same applies to most of the effects of drugs on children or the fetus, a population subgroup in which pre-marketing experimental studies are not being conducted [3].

Post-marketing surveillance

The term pharmacoepidemiology emphasizes the use of epidemiologic thinking and methods regardless of the phase of drug development. Post-marketing surveillance refers to a specific time in the life of a drug: the time span that begins when a drug is introduced to the market (also known as phase IV). The need for post-marketing surveillance studies arises from the limitations of pre-marketing clinical trials. Although the randomized, controlled clinical trial is the most powerful tool available to researchers, its limitations due to ethical, practical and economic reasons should be recognized. In such trials, patients are followed for short periods and under very strictly defined conditions (frequent and thorough examinations, fixed dose regimens, tertiary care hospitals, etc.). Hence, when marketing approval of a new drug is granted by the appropriate regulatory authority, thousands of individuals become exposed to the drug in a variety of sociological, cultural and clinical settings. Furthermore, the therapeutic use of drugs is often extended to population subgroups not included in the pre-marketing studies, to new indications emerging in clinical practice, and for periods much longer than those covered in most clinical trials. In the actual world, patients present a wide range of diagnoses, comorbidity, lifestyles, and exposure to other drugs [1].

Phase IV studies provide additional information on the benefits and the risks of drugs. In Phase IV studies, larger and more heterogeneous populations are usually available, and a stronger emphasis is placed on reproducing the usual clinical care conditions. Sample size is a direct determinant of the probability of detecting drug effects that occur with a low incidence. In order to detect an unintended drug effect the number of subjects that need to be followed is three times that of the estimated incidence of the event. Hence, the larger sample sizes used in Phase IV studies enable drug effects with a low incidence to be assessed.

Adverse Drug Reactions — Clinical and Economic Aspects

Some definitions of terms would be helpful here [4].

- *Adverse event* — as defined by the World Health Organization: "...any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function."
- *Adverse Drug Reaction (ADR)* — an adverse drug reaction is suspected if a detrimental and unintended reaction observed in the patient is connected in terms of time with the administration of the drug and has evidently not been brought about by any other cause than the administration of this drug.
- *Serious adverse reaction* — a life-threatening or disabling event, requiring hospitalization or medical intervention, or resulting in death or congenital anomaly.
- *Unexpected adverse reaction* — an event not listed in the labeling of the product, or of greater severity or specificity.
- *Signal* — reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Drug-related morbidity and mortality have been estimated in the USA to be more than 136 billion dollars annually [5]. These estimates are higher than the total cost of cardiovascular care or diabetes care in the U.S. A major component of these costs is adverse drug reactions. According to the Harvard Medical Practice Study, which reviewed over 2,671,863 patients discharged from several hospitals in the state of New York during the mid-eighties, at least 3.7% of all hospitalized patients developed serious, disabling, and clinically important adverse events [6]. In a meta-analysis of four databases containing data from 1966 to 1996, it was found that the overall incidence of serious ADRs was 6.7%, and that of fatal ADRs 0.32% of hospitalized patients. This led to the estimation that in 1994, a total of 2,216,000 hospitalized patients had serious ADRs and 106,000 had fatal ADRs, making ADRs between the fourth and sixth leading cause of death in hospitalized patients in the U.S. [7]. Another study, conducted in a tertiary hospital, found that the extra length of hospital stay attributable to ADRs was 1.74 days, and the excess cost of hospitalization attributable to ADRs was $2,013. The authors concluded that an ADR is associated with a significantly prolonged length of stay, increased economic burden, and an almost twofold increase in the risk of death [8].

Adverse drug reactions — reporting and monitoring

Effective post-marketing surveillance is dependent on the availability of information on possible hazards associated with medicines in a representative population under conditions of normal clinical use. It requires a system for collecting and monitoring suspected adverse drug reactions, as well as processes for reviewing the many signals identified and deciding whether further investigation is necessary. All potentially important hazards need to be investigated with a view to appropriate remedial action based on sound scientific data. Various methods, particularly spontaneous ADR reporting, provide signals of potential hazards. Formal pharmacoepidemiological studies, where available, are important to confirm or clarify such signals. The most important outputs of the process are actions to

optimize safe use of medicines and provide information to health professionals and patients on their use [9].

The FDA relies on voluntary reports from health care professionals, yet despite the volume of reports it is clear that these reports are only a fraction of the ADRs encountered by health providers [10]. It was estimated that in the eighties only about 1% of serious events was reported to the FDA [11]. In 1993, the FDA introduced MEDWatch as a new approach to reporting adverse effects of a medication or device. This effort by the FDA was aimed at both augmenting the awareness of health care professionals to ADRs and emphasizing the importance of reporting [10].

Most western countries have developed and implemented a national ADR reporting and monitoring program. For example, the German Regulations on this issue state that:

> In the interest of prevention of direct or indirect hazards to human or animal health, it shall be the responsibility of the competent authority to record and analyze those risks occurring during the administration of drugs, in particular in respect of side effects, interaction with other products and contra-indications, and to coordinate the measures to be adopted in accordance with the law. For this purpose, the competent authority shall act in cooperation with the agencies of the World Health Organization, the drug authorities of other countries, the associations of health professions and others who, in the execution of their work, keep records on drug risks. The Ministry of Health should draw up a graduated plan detailing the execution of the tasks indicated above. In this plan, the cooperation between the authorities and services involved at the various danger levels as well as the intervention of the pharmaceutical manufacturers shall be specified, and the various measures to be taken in compliance with the provisions of this law shall be determined. [Dejas-Eckertz P. Bundesinstitue fur Arzneimittel und Medizine Producte (BfArM), personal communication, 1999]

The World Health Organization has established an International Collaborative Monitoring Center in Uppsala, Sweden, which operates an international database (holding more than 1.5 million reports) to which most countries with an established spontaneous reporting scheme report their data [4]. Local ADR programs for health care institutions have also been suggested in the U.S. The American Society for Health-System Pharmacists has declared that:

> Every health care system should develop a comprehensive, ongoing program for monitoring and reporting ADRs. Such programs encourage ADR surveillance, facilitate ADR documentation, promote the reporting of ADRs, provide a mechanism for monitoring the safety of drug use in high risk patient populations, and stimulate the education of health professionals regarding potential ADRs. A comprehensive, ongoing ADR program should include mechanisms for monitoring, detecting, evaluating, documenting and reporting ADRs, as well as intervening and providing educational feedback to prescribers, other health care professionals and patients. [12].

In conclusion, every drug has the potential to do harm. Adverse drug reactions are frequent and may be fatal, but only a few of them can be detected during the premarketing period of the drug's development. It was shown that ADRs are a leading cause of death; they increase the length of hospitalization, mortality and morbidity, and cause an immense economic burden to society. In order to minimize the impact of ADRs, monitoring and reporting programs have been established either as local or national programs in most western countries. However, ADRs are still not recognized as a "disease state" that requires treatment. In view of the fact that awareness among health care professionals, policy makers and the public is still relatively low, it is our responsibility as health care professionals to disseminate the need for reporting adverse drug reactions.

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