Excessive use of drugs and adverse events

Epidemiologic and pathogenetic aspects

A. Kansky

ABSTRACT

Background. An unwarranted increase in the prescription and intake of drugs can be observed in the developed countries. The data on the incidence of adverse drug events is not reliable, but estimated to be close to 10%. Most drug eruptions affect the skin and are not life-threatening, but some very serious adverse drug events also occur. The cost of the drugs themselves, as well as the treatments, are becoming a burden on both insurance company and state budgets.

Underlying causes of the excessive use of drugs. Information about drug usage may be partially biased. One effect of intensive and costly research has been to increase the supply of drugs. Articles in the popular press, advertising and also the sponsorship of congresses and symposia by drug manufacturers may also be seen as contributing to the awareness of and excessive use of drugs. Those involved in the misuse of drugs are frequently those most highly affected by the stress of modern life, psychopathic personalities, and drug addicts.

Mechanisms by which adverse drug events are provoked. Allergic, non-allergic and pharmacogenetic mechanisms as well as drug overuse, toxic effects and the incompatibility of different drugs taken together are the most frequent trigger factors.

Means by which the number of adverse drug events may be reduced. Adverse drug events may be reduced given the dissemination of correct information, through controlled clinical studies, through a strict editorial policy by the editors of medical journals, through an epidemiological approach to the phenomenon of adverse drug events, through pharmacogenetic studies, through appropriate reaction to biased data, and through general education in the sense of making the patient more aware and more careful of their psychic and physical condition.

KEY WORDS

drug eruptions, adverse drug events, biased information, provoking mechanisms, allergic, non-allergic, pharmacogenetics, epidemiology, fostering factors, prevention, recreation facilities

Introduction

Excessive use of drugs presents itself as a major contemporary problem in the developed countries. Many people see their doctor or are even admitted to hospital because of *adverse drug reactions (ADR)*. Some authors prefer the term *adverse drug events (ADE)* taking the latter expression to include both adverse drug reactions and various other toxic phenomena. Skin manifestations triggered by drugs are frequent, and are generally referred to in dermatological literature as *drug*

Table 1. Listed are professional groups or bodies collecting epidemiologic data on drug eruptions.

Adverse Reaction Collaborating Centre	WHO Upsala
Yellow Card Reporting System	United Kingdom
Pharmacovigilance	France
Adverse Drug Reaction Reporting System	Food and drug Administration USA
Adverse Drug Reaction Reporting System	Amer Acad Dermatol
Gruppo Italiano Studii Epidemiologici in Dermatologia	Italy
Reporting Systems by Pharmaceutical Companies	
Various National Schemes	

eruptions. The offending drugs have either been prescribed by medical professionals, are available over-the-counter, or have been obtained through individual initiative.

The incidence of ADEs is estimated at 10-20% (1,2), but the information is incomplete, even in the developed countries. This dearth of adequate documentation is due to the lack of time of doctors, the lack of suitable questionnaires, and also due to diagnoses that have not been confirmed by laboratory tests as well as for fear of possible litigation. Years ago, interested persons started to collect data on ADEs on their own initiative; in the present situation, however, the problem is dealt with in many countries by professional groups and official institutions.Table1.

Different methods have been employed for the collection of data, and they share different advantages and disadvantages. The most efficient is the so-called intensive system, which has enabled the detection of up to 100% of ADE cases. Unfortunately only small groups of patients can be studied in this way (3,4).

Another big problem created by the extensive use of drugs is the high cost to the budgets of both states and health insurance companies. According to a report based on a hypothetical cohort of ambulatory patients, the overall cost of *drug related morbidity and mortality* in the USA was estimated at $177 billion for the year 2000 (3).

Underlying causes of the excessive use of drugs

Advances in biochemistry, immunology, molecular biology and other basic sciences offer unprecedented opportunities to both scientists and their employers to develop new drugs. The high cost of introducing new means of preparing drugs, when considered as a commercial proposition within a highly competative market, have forced both companies and all the subjects involved to market such products as soon as possible. To illustrate this tendency I would like to cite the current trends in the systemic treatment of psoriasis.

Immunosuppressive treatments including metothrexate, hydroxyurea, cyclosporin, mycophenolic acid, 6-thioguanine and even pimecrolimus are familiar to dermatologists, and the same can be said for metabolic preparations like psoralens, acitretin and 13-cis retinoic acid (5,6,7). A series of new biological and immunological substances which suppress inflammation have been introduced (8). *Alefacept* inhibits the release of inflammatory cytokines from CD4 and CD8 effector cells (9), *efalizumab* interferes with the lymphocyte function associated antigen 1 (LFA-1) and thus inhibits binding with the ligand intercellular adhesion molecule-1 (ICAM-1) (10). *Etanercept* (11), a human dimeric fusion protein, blocks the receptors for the tumor necrosis factor α (TNF α). *Infliximab* (12) is a chimeric antibody composed of a murine variable and a human constant part of IgG 1/α that binds to TNF molecules. There are reports on 16 cases of ADEs after infusions of infliximab (13). A number of further substances like adalimuab, baxaroten, onercept, simulect or zorcell (IR 502) are either in development or already entering the market. At the moment it is not possible to foresee the eventual long range ADEs that will involve the lymphatic system.

A further and compelling reason for the overuse of drugs must be attributed to the attitude of a *consumer society* and the *suggestibility* that prevails among the general population. Unstable persons, hypochondriacs, neurotics and maniacs and also a substantial number of otherwise normal people believe that drugs can solve their problems. The high level of stress in everyday life in the developed countries is responsible for a number of psychosomatic disorders like hypertension, gastric ulcers and psoriasis among others.

A part of the responsibility for this must lie with pharmaceutical companies that employ sophisticated propaganda and advertising, as well as with those members of the medical profession who succumb to such publicity. It must be admitted that pharmaceutical companies are the major sponsors of medical books and periodicals, and of congresses and symposia as well as for supporting participants and speakers at such gath-

Table 2. Drug reactions in persons with genetic deficiencies, triggered by drugs.

Disease	Deficient enzymes or proteins	Incriminated drug
lupus erythematosus	slow acetilation	procainamid (arrhythmia) hydralazin (hypertension)
hemolysis	glucose 6 phosphate dehydrogenase	aspirin, antimalarials, sulfonamides, dapson, vicia fava, nitrofurantoin
methemoglobinemia	pathologic Hb (HbM)	nitrates, nitrites, aniline, sulfonamide, antimalarials, dapson
porphyriae, various types	↑ ALA synthetase, ↓ferro-chelatase, ↓PBG deami-nase, ↓UPG decarboxylase	barbiturates, alcohol, chloroquine, estrogens
apnoe, suxamethonium sensitivity	deficient pseudocholin-esterase	suxamethonium

ALA delta aminolevulinic acid
PBG porphobilinogen
UPG uroporphyrinogen

erings. Undoubtedly they make valuable contributions to the level of medical and biological education and to the exchange of ideas, but through this generosity they acquire for themselves ample opportunity to promote their own interest and what must be seen as one-sided information.

And finally, any such partial or even biased information on health problems and drugs is disseminated through newspapers, magazines and various periodicals. As a general rule, people prefer to read articles on medical topics that have been prepared by non-professionals: it makes for interesting and easier reading, but it is often over-simplified and not exact.

Mechanisms of adverse drug events

It is widely known that the majority of ADEs are of *allergic origin*. Specially in acute allergic ADEs the IgE attached to mastocytes play a crucial role. There are reliable tests for the assessment of total as well as of certain specific IgE. On the other hand, the IgG may bind to the antigen and thus inhibit the allergic reaction. The *cellular response* (delayed type response) seems to play a major role in cutaneous ADRs (*drug eruptions*). T lymphocytes, receptors, mediators, interleukines, signalling and transcription molecules are the main factors. On the molecular level these events are highly complicated.

Toxic (nonallergic) ADEs are provoked by the direct toxic action of a drug or its metabolite primarily on enzymes, but also on the other above-mentioned factors. They are mainly provoked by a dose of the drug that is excessive, or a genetically deficient enzyme.

Photoallegic and *phototoxic ADE* represent another category of side effects (15).

Genetically induced ADEs are usually severe and even life-threatening, and research in molecular biology deserves credit for the two new fields that have been introduced. *Pharmacogenetics*, which deals with DNA mutations and their influence on the expression of enzymes, transporting molecules, receptors and further factors, and *pharmacogenomics,* which is concerned with investigation to which extent such pharmacogenetic changes influence the pharmacodynamics and pharmacokinetics of drugs.

The following examples may be helpful for a better understanding of the problem.

In persons affected by deficient enzymes of porphyrin synthesis, drugs or substances like barbiturates, estrogens, alcohol or lead induce *porphyria*. The disease type itself depends on the enzyme involved. For example, deficient ferrochelatase causes erythropoietic protoporphyria (15,16,17). Diaminodiphenylsulfon (dapson) triggers methemoglobinemia in patients deficient in glucose-6-phosphate dehydrogenase activity (18). Table 2. Familial hypercholesterolemia is caused by hyperproduction of choleesterol and the inability to synthesize LDL receptors. Statins inhibit the enzyme β-hydroxy-β-methyl coenzyme A reductase and indirectly increase the number of hepatic LDL receptors. Unfortunately, in such cases, severe ADEs like myopathy or rabdomyolysis may develop (19). Antipsychotics used in psychoses and psychoneuroses may provoke ADEs in certain patients (20). Acute allergic ADRs may appear even during treatment with cytostatics like epirubicin (21) or carboplatin (22). Transporter protein like MDR1 is a glycoprotein involved in drug resistance of tumor cells and confers intrinsic resistance to tissues by exporting toxic exogenous substances. Genotyping of MDR1 may become important in the future individualized pharmacotherapy (23).

ADEs occur relatively frequently after the intake of

Table 3. Naranjo Adverse Drug Reaction Probability Score. Clin Pharmacol Ther 1981: 30: 239-45

Questions	Yes	no	unsure
Previous conclusive reports on this reaction	+1	0	0
Did ADR appear after the drug was administered	+2	-1	0
Did ADR improve when the drug was discontinued or a specific antagonist was given	+1	0	0
ADR appearance after drug readministration	+2	-1	0
Are there alternative causes other than the incriminated drug	-1	+2	0
Did ADR appear after placebo	-1	+1	0
Drug detected in blood (fluids) in toxic concentration	+1	0	0
ADR more severe with large dose, less severe with small dose	+1	0	0
Similar ADR to same or similar drug in past exposure	+1	0	0
ADR confirmed by objective evidence	+1	0	0
Total score			

ADR probability scale score: 0 – doubtful, 1 – 4 possible, 5 –8 probable, >9 definite

analgesics or nonsteroid anti-inflammatory drugs. They range from benign exanthematous drug eruptions to life-threatening toxic ADEs. *Paracetamol (acetaminophen*) in a dose of 0.5-1.0 gram up to 4 times daily, has analgesic, antipyretic and weak anti-inflammatory effects. It may be given alone or in combination with another analgesic, often with aspirin or codein (24). Acute allergic ADRs (25), and also sever hepatocellular necrosis and granulomatous lesions have been reported, and caused by higher dosages or prolonged intake (26).

Diagnostic possibilities

Great efforts have been made to devise tests suitable for the detection of the drug held responsible for causing the ADR, but unfortunately the majority of these are not precise enough. Positive total and specific IgE tests strongly support the diagnosis of allergic ADR, while a number of toxic ADEs caused by genetic deficiency can be confirmed by biochemical tests. Intradermal and scratch tests with drugs are potentially dangerous and many doctors try to avoid them, in which cases patch testing may be sometimes useful (27). Immunogenetic tests are mostly highly complicated and still in the stage of development.

In view of such diagnostic difficulties the epidemiologic approach is favored by many clinicians. Data on ADEs are collected and ordered according to the clinical manifestation or according to the drug that is held responsible. Useful data, that is suitable for clinical work may be found in manuals such as the short and practical work by Bruinsma (28) or the more extensive study by Litt (29).

Diagnostic algorithms have been proposed in the attempt to verify the offending drug. The basis of such an approach is to have made a sufficiently large collection of epidemiologic data on ADEs including patients' histories, drugs found responsible, and types and grades of the ADEs observed. A special questionnaire has to be prepared, and data on those patients suspected to be affected with an ADE entered. On the basis of the score yeilded by the questionnaire it would be possible to make a decision concerning the suspected drug. Table 3. An example of the application of the *Naranjo ADR probability scale score* (30) is shown in the study done by Hafner (4). Among 13004 patients of an emergency department involved in the study, 321 were screened for a possible ADR, and in 217 of them the score of >4 was obtained, in effect supporting the diagnosis. The study revealed that the most frequent offending drug was *insulin*, followed by the anticoagulant *warfarin*, diuretic *furosemid*, various *chemotherapeutics* and by other drugs.

The *global index of safety (GIS)* is a further algorithm which allows for the comparison of the relative safety of two or more drugs. Symptoms observed in patients are graded, entered in a special questionnaire, scored and the GIS was calculated therefrom. Sacristan et al investigated antipsychotics and found that *olanzapin* caused less ADRs than *riperidon or haloperidol* (31).

Means by which the number of adverse drug events may be reduced

In developed countries a number of safety regulations have been implemented to keep the number of ADEs at a relatively low level: preclinical and clinical

studies, the registration of drugs, the insertion of guidelines into drug packaging, the institutional monitoring of ADEs and others. In view of the fact that that ADEs may become evident only years after a drug has been used, *postmarketing surveillance of ADEs* is suggested. Clinical studies including patients have to be approved by an ethical commission. Editors of medical journals are supposed to accept for publication only clinical studies in which patients were selected randomly, studies that include a reasonable number of patients and control persons and that have been statistically evaluated. All authors are required to declare their financial interests. In cases where ADEs are suspected the necessary tests on patients have to be done.

ADEs may also be reduced by means of the introduction of *personalized medicine,* which anticipates the screening of patients for immunologic and metabolic incompatibilities, prior to the drug intake. This kind of policy foresees the introduction of new sophisticated tests, especially in the field of immunogenetics, like DNA microarrays or DNA chips (30,31).

To educate and warn the general population not to use drugs indiscriminately, is important. Editors of newspapers and magazines should be asked to publish only reliable information on drugs. Any biased or incorrect information must be able to be identified and countered immediately by a competent authority. People have to be encouraged to try to solve minor health problems by adopting adequate habits or by exercising. The bodies planning new settlements should foresee sport and recreation facilities. And a certain degree of responsibility must lie with the authorities and politicians.

Conclusion

The problem of overuse of drugs and ADEs is a substantial and complex issue, and it is difficult to find an adequate solution. The primary responsibility to combat ADEs must lie with health authorities and drug companies. New fields of research such as the epidemiology of ADEs, pharmacogenetics and pharmacovigilance are expected to play an essential role in controlling ADEs. The role of the medical profession itself can only be limited, the essential emphasis being to educate patients and the general population.

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A U T H O R ' S A D D R E S S *Aleksej Kansky MD, PhD, Professor of dermatology, Dept of Dermatology, Zaloška 2, 1525 Ljubljana, Slovenia*