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The Value of Reporting Therapeutic Ineffectiveness as an Adverse Drug Reaction

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Abstract

Therapeutic ineffectiveness is a frequent drug-related problem that can occur in a variety of different situations and be caused by different mechanisms. Examples are inappropriate use, interactions or metabolic abnormalities. Observations in patients of unexpected ineffectiveness can provide important information with regard to such situations. Therefore, ineffectiveness – especially when unexpected or unexplained – is a potentially important reportable event in pharmacovigilance. The terms regarding ineffectiveness in the WHO Adverse Reaction Terminology (WHOART) have been recently revised in order to enable optimal coding of such case reports.

Obviously there are limitations to the therapeutic power of medical drugs. For many diseases there is still no cure available and many people die when the failure of one or more vital function can no longer be redressed by therapeutic measures. An adverse reaction is defined as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man'.[1] Although from the pharmacological point of view perhaps not a true adverse effect, therapeutic failure may well be noxious and unintended, and is probably one of the most frequent drug-related problems. In a study of drug-related hospital admissions (internal medicine and intensive care) drug-related problems accounted for 16% of admissions, of which more than half (55%) referred to therapeutic failure.[2]

The early detection of unforeseen adverse drug reactions and interactions is the major objective of pharmacovigilance. In a recent guideline for the running of a pharmacovigilance centre produced by the World Health Organization, the 'estimation of quantitative aspects of risks and benefits of drugs' is specifically mentioned as one of the goals.[3]

In this paper we review the phenomenon of insufficient therapeutic effect in the context of pharmacovigilance.

1. Efficacy and Effectiveness

The controlled clinical trial is the method of choice to demonstrate – qualitatively and quantitatively – the efficacy of a medicine. In a discussion on what society wants from medicines, a distinction was drawn between the way in which a medicine works under clinical trial conditions and how it may work in everyday use.[4] The 'efficacy' of a medicine concerns the level of improvement and

Table I. Reasons for reporting ineffectiveness in pharmacovigilance

Pharmaceutical defects
counterfeit drug
generic or magistral drug with low bioavailability
mishandling of drug (storage, transportation)
Interactions (inhibition of reported drug)
decreased absorption
enzyme induction
stopping of enzyme inhibiting drug
Inappropriate use (non-compliance)
wrong dose
wrong duration
wrong indication
Resistance
infectious diseases
disease transmitting vector
tumour cells
ineffective batch (for vaccines)
genetic alteration (for vaccines)
pharmacogenetic resistance (e.g. rapid metabolism, coumarin resistance)
Tolerance and tachyphylaxis (e.g. enzyme induction, opioid tolerance)
Early effectiveness monitoring (e.g. disappointing response rate in patients after marketing)
Long term effectiveness monitoring (e.g. waning of effect during prolonged use)

the proportion of responders in a well-defined and selected population, whereas 'effectiveness' refers to the performance of the drug in a 'real-life' population. Using these terms defined in this way, an efficacious drug can for several reasons be ineffective in a given patient.

2. Ineffectiveness

The anecdotal reporting of ineffectiveness is unlikely to influence the body of knowledge produced by the clinical trials with the drug. When ineffectiveness is a likely natural occurrence in the context of the disease treated, the type of medicine used, or the clinical status of the patient, its reporting to a pharmacovigilance centre may make little sense and may be a waste of time. However, the unexpected occurrence of the absence, decrease or change of effect may be indicative of a variety of interesting and important underlying problems or processes, relevant to pharmacovigilance (table I).

2.1 Pharmaceutical Defects

Unexpected ineffectiveness may be secondary to poor pharmaceutical quality of the drug, e.g. in the case of magistral production (i.e. in a dispensing pharmacy), a generic product with low bioavailability or a counterfeit drug. The possibility of the latter is nowadays a reality and occurs in all parts of the world.[5] Also inappropriate handling of a drug, e.g. during storage or transportation, may explain unexpected therapeutic failure.

2.2 Interactions

Likewise, the unexpected decrease or absence of a therapeutic effect may be indicative of an interaction with another medicine, occupational chemical, food or 'social drug'. In this way both enzyme induction or enzyme inhibition (leading to increased breakdown of the drug in question after discontinuation of the interacting drug) may be discovered. In addition, several drugs impair the absorption of other drugs. Also the use of alcohol, smoking or dietary habits may change the absorption or effect of medical drugs.

2.3 Inappropriate Use

A common cause of therapeutic ineffectiveness is the inappropriate use of a drug, e.g. 'non-compliance' with the instructions for use. A wrong indication, use for too short a time, use of too low a dose, or unrealistic expectations may all explain for the absence of the expected effect.

2.4 Resistance

Resistance against the action of a drug can be pre-existing or acquired and be partial or total. There are many drugs that are less effective in people who are genetically determined 'fast metabolisers'. Sometimes the unexpected absence of effect of an otherwise strong acting drug can be explained by a rare genetic abnormality (e.g. familial coumarin resistance).

Ineffectiveness may be caused by the development of resistance of a micro-organism or tumour to the actions of the drug. Also, resistance of disease

spreading vectors (e.g. mosquito) against repellents may occur. The detection of the development of resistance of malaria, retrovirus, bacterial strains or carcinoma of the prostate are major concerns of pharmacovigilance. Inefficacy of vaccines may take different forms, e.g. insufficient immunogenicity (ineffective batch), antigenic alteration of the microorganism (virus) or programmatic error (storage, dose, administration), and needs special attention to be detected and evaluated.

2.5 Tolerance and Tachyphylaxis

For several drugs it is known that, due to adaptive processes in the body of the recipient, their effect decreases over time (several days to weeks). This is known as tolerance. Tolerance may be pharmacokinetic (e.g. enzyme induction), pharmacodynamic or 'learned'.[6] To maintain the level of effect, a steady increase in dose of these drugs is needed. Tolerance is known to particularly occur with drugs of addiction (notably opioids), and cessation of the drug may be followed by a withdrawal reaction. In the literature the words resistance and tolerance are sometimes used as synonyms, and it may not always be easy to differentiate between them. Enzyme induction by alcohol use, for example, may explain relative resistance to thiopental anaesthesia.

Tachyphylaxis refers to the situation where the repeated administration of a drug for a short period of time is followed by a temporary insensitivity of the recipient to its effect. It may have different underlying mechanisms.

In addition, there are other possible situations where the reporting of ineffectiveness may be important.

2.6 Early Effectiveness Evaluation

New drugs are studied in selected patients and under controlled conditions. Sometimes, following launch, a drug is found to be effective in a smaller proportion of users than was predicted in the original trials, or to be ineffective in certain subpopulations. Dose finding studies may have been insufficient or the selected trial patients may have been comparatively easy to treat. Case reports of ineffectiveness may be helpful in the early detection of such problems.

2.7 Long Term Effectiveness Evaluation

Clinical trials are, as a rule, of limited duration. Therefore, there may be some uncertainty with regard to the sustainability of effect over long periods of time. Spontaneous reporting may detect a possible decrease in effectiveness after the prolonged use of a drug.

3. Reporting Ineffectiveness

A therapeutic response may be weak or absent, have a delayed onset, be of short duration or may decrease or disappear after a period of satisfactory

Table II. WHO Adverse Reaction Terminology (WHOART) terms regarding ineffectiveness (1998 version)[7]

System organ class	High level term	Preferred term	Included term
Body as a whole	Therapeutic response decreased	Therapeutic response decreased	Bacterial resistance
Body as a whole	Therapeutic response decreased	Therapeutic response decreased	Efficacy, lack of
Body as a whole	Therapeutic response decreased	Therapeutic response decreased	Light anaesthesia
Body as a whole	Therapeutic response decreased	Tolerance increased	Tachyphylaxis
Body as a whole	Therapeutic response decreased	Therapeutic response decreased	
Body as a whole		Tolerance	Tolerance development
Body as a whole	Therapeutic response decreased	Tolerance increased	Tolerance increased
Body as a whole		Tolerance	
Reproductive disorders, female	Pregnancy unintended	Pregnancy unintended	Pregnancy while receiving oral contraceptives
Reproductive disorders, female	Pregnancy unintended	Pregnancy unintended	Pregnancy with IUD

IUD = intrauterine device.

Table III. Revised WHO Adverse Reaction Terminology (WHOART) terminology for the coding of therapeutic ineffectiveness

System organ class	High level term	Preferred term	Included term
Body as a whole	Medicine ineffective	Medicine ineffective	Anaesthesia insufficient
Body as a whole	Medicine ineffective	Medicine ineffective	Drug ineffective
Body as a whole	Medicine ineffective	Medicine ineffective	Effect, lack of
Body as a whole	Medicine ineffective	Medicine ineffective	Inefficacy
Body as a whole	Medicine ineffective	Medicine ineffective	Ineffectiveness
Body as a whole	Medicine ineffective	Medicine ineffective	Therapeutic failure
Body as a whole	Medicine ineffective	Medicine ineffective	Therapeutic response delayed
Body as a whole	Medicine ineffective	Medicine ineffective unexpected	Medicine ineffective unexpected
Body as a whole	Medicine ineffective	Resistance	Resistance, infectious agent
Body as a whole	Medicine ineffective	Resistance	Resistance, metabolic
Body as a whole	Medicine ineffective	Tachyphylaxis	
Body as a whole	Medicine ineffective	Therapeutic response decreased	
Body as a whole	Medicine ineffective	Tolerance	
Reproductive disorders, female	Pregnancy unintended	Pregnancy unintended	Pregnancy while receiving oral contraceptives
Reproductive disorders, female	Pregnancy unintended	Pregnancy unintended	Pregnancy with IUD

IUD = intrauterine device.

use. The notions of inefficacy, lack of effect, ineffectiveness, tachyphylaxis, tolerance, resistance, therapeutic response decreased or therapeutic failure may refer to more or less different situations. In table II the terms referring to various forms of ineffectiveness are listed as they are used in the 1998 version of WHO Adverse Reaction Terminology (WHOART),[7] the adverse event terminology used by the Uppsala Monitoring Centre (UMC) in the World Health Organization's programme for international drug monitoring. Pregnancy that occurs despite contraceptive treatment is a distinct form of ineffectiveness for which special preferred terms have been included (table II and III). In addition, there are a number of preferred terms referring to the aggravation of a pre-existing disease, e.g. depression, diabetes mellitus or epilepsy (e.g. 'depression aggravated'), that also may indicate a therapeutic failure. These latter terms are not reviewed in this paper. Such reports sometimes refer to the situation where a second drug has interfered with the original treatment of the disease, i.e. to drug-drug interactions. In the case of an interaction, the suspected drugs should be coded as such, i.e. as I (interaction) instead of S (suspected) or O (other), according to the instructions provided by the UMC.[8]

In order to ease the coding of the various situations that may occur, we have revised this part of WHOART, as shown in table III. In addition, we recommend that National Pharmacovigilance Centres add a clear 'free text' description of what has happened to the patient.

4. Implications

As a method, spontaneous reporting is of little use in the study of the efficacy of medical drugs. Anecdotal reports of ineffectiveness are unlikely to alter the body of evidence produced by clinical trials. Observations in patients regarding unexpected ineffectiveness, on the other hand, may be of great importance in pharmacovigilance, particularly in situations when (at first sight) the mechanism is obscure. Ineffectiveness may be an early warning of a variety situations, shown in table I, which may lead to decreased therapeutic usefulness of a drug. A good understanding of these situations is needed to ensure effectiveness of and adherence to treatment. Whether it is a true adverse effect or not, unexpected therapeutic ineffectiveness is an important event to be reported in pharmacovigilance.

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