CURRENT OPINION

Drug Safety 2002; 25 (7): 485-487
0114-5916/02/0007-0485/$25.00/0

Therapeutic Ineffectiveness
Heads or Tails?

Albert Figueras,[1] *Consuelo Pedrós*,[1] *Mabel Valsecia*[2] and *Joan-Ramon Laporte*[1]

1 Fundació Institut Català de Farmacologia. Departament de Farmacologia, Terapèutica i Toxicologia, Universitat Autònoma de Barcelona, Barcelona, Spain
2 Regional Pharmacovigilance Centre of the Northeast of Argentina, Departamento de Farmacología, Universidad Nacional del Nordeste, Corrientes, Argentina

Abstract

Reporting of therapeutic ineffectiveness through adverse drug reaction spontaneous reporting systems has been proposed by some authors. In the WHO Adverse Reactions Terminology (WHO-ART) and Medical Dictionary for Regulatory Activities (MedDRA) terminology, the term therapeutic ineffectiveness includes drug interactions, resistance, tolerance and tachyphylaxis, as well as pharmaceutical defects such as substandard, adulterated, and counterfeit drugs.

Under certain circumstances, reporting therapeutic ineffectiveness may contribute to identifying pharmaceutical defects. However, the best approach to avoid their occurrence would be implementing good manufacturing practices and strengthening quality control activities. This would prevent the misuse of spontaneous reporting of adverse drug reactions (e.g. when reporting of therapeutic ineffectiveness is 'suggested' by interested parties, especially when a generic product has been substituted for a branded original product).

'Medicine ineffective' is a term of the WHO Adverse Reaction Terminology (WHO-ART) used by the Uppsala Monitoring Centre in the WHO's Programme for International Drug Monitoring. It includes terms such as 'inefficacy' and 'ineffectiveness', 'lack of effect', 'therapeutic failure' and 'therapeutic response decreased', 'resistance' (both metabolic and to an infectious agent), 'tachyphylaxis', 'tolerance', 'anaesthesia insufficient' or 'pregnancy while receiving oral contraceptives'.[1] The new Medical Dictionary for Regulatory Activities (MedDRA)[2] also includes 'therapeutic ineffectiveness' as a preferred term.

Recently Meyboom et al.[3] have upheld that reporting about the absence, decrease or change of effect is a way to identify a number of important underlying problems or processes, relevant to pharmacovigilance. As defined by these authors, in pharmacovigilance therapeutic ineffectiveness includes several situations potentially relevant for the patient. An analysis of these terms shows a tangled landscape, heterogeneous both in its causes and consequences. Most of the concepts included in the term therapeutic ineffectiveness clearly concern pharmacovigilance (e.g. interactions, resistance, tolerance, and tachyphylaxis). However, some of the included terms deserve special consideration, because their inclusion in a surveillance scheme such as spontaneous reporting could favour misuse of the programme itself. This is especially true when therapeutic ineffectiveness is suspected to be due to counterfeit drugs or products of substandard quality, mishandling of drug storage or drug transportation, or use of expired drugs.

The latter cases share an additional common feature: they are pharmaceutical defects – and so, are qualitatively and aetiologically different from therapeutic failure or a decreased or delayed therapeutic response due to pharmacokinetic or pharmacodynamic problems. Furthermore, they are avoidable with good quality control policies and good pharmacy practices. So, reporting therapeutic ineffectiveness due to pharmaceutical defects as an adverse drug reaction has pros and cons.

For the physician with a patient who has unexpectedly not responded to treatment or in whom the therapeutic response is delayed, it is difficult to know whether the patient: has taken the prescribed drug but has not responded to it; has not taken the medication as advised; or has taken a drug with a pharmaceutical defect.

The actual effectiveness of a drug depends on each one of the links of a long chain of processes: manufacturing, regulation, quality control, promotion, distribution, prescribing, dispensing, and use. The latter implies a pharmacokinetic/pharmacodynamic interaction between an individual patient and a particular drug. Populations in less developed countries are at special risk of a defect in any of the links on this chain,[4,5] although, as suggested by the recently published report 'Fake prescription drugs are flooding the United States', the problem of counterfeit drugs is not only limited to less developed countries.[6]

In this scenario, counterfeit and substandard drugs are failures of quality control. Absence of a tradition of good manufacturing practices (GMPs), coupled with an ineffective licensing system and lack of government regulations and controls over drug manufacturing, importation, storage, supply, and sale of drugs facilitate the appearance of defective pharmaceutical products.[7] The WHO advice to governments on generics is that they should: (i) provide clear, firm, and equitable legislation that addresses all the relevant issues and carries appropriate sanctions for violations; (ii) provide support in the form of financial and other resources that are commensurate with the designated functions, particularly in relation to staffing and other resources for the GMP inspectorate and quality control laboratories; (iii) provide advocacy in the political arena, and particularly a willingness to defend decisions and policies which may be unpopular with vested interests but which are to the benefit of public health, and; (iv) provide support when legislated sanctions are imposed for violations of legislation.[8] Thus, the challenge is actively promoting more effective regulatory decisions, rather than promoting the reporting of cases of therapeutic ineffectiveness

One reason against actively promoting reporting of therapeutic ineffectiveness in a broad sense (i.e., including pharmaceutical defects) to adverse drug reaction surveillance schemes is the potential misuse of the scheme. In several less developed (and also more developed) countries where healthcare systems with limited and closed lists of financed drugs exist, we have seen that the substitution of a well-established original brand-name drug by a generic drug has been followed by an 'epidemic' of reports of therapeutic ineffectiveness of the generic product. Interestingly, the reports had been sent from hospital wards or by physicians who had never reported before, as usually happens when reporting is specifically stimulated.[9] It is easy to imagine someone from a firm 'damaged' by a particular substitution in the official list of reimbursable or financed medicines promoting *sotto voce* the reporting of generic ineffectiveness.

Finally, it is worth remembering that therapeutic efficacy is merely a higher probability of clinical improvement, compared with placebo. Therefore, in routine practice 'inefficacy' is a common and necessarily coexisting situation, and it does not imply 'rare' or 'exceptional' circumstances, except for several well defined illnesses or drugs (e.g. anaesthetics or hormonal contraceptives).

The establishment of a permanent 'Observatory of Drug Quality' by WHO in collaboration with organisations involved in the provision of essential drugs (e.g. UNICEF, World Bank, the European Union and non-governmental organisations), has been proposed. The Observatory would oversee

the implementation of adequate and effective control procedures.[10] This proposal followed the WHO recommendations regarding the measures to be co-ordinated on a global basis against counterfeit and substandard drugs, which include actions to be taken by drug regulatory authorities, the WHO, and pharmaceutical manufacturers.[11] This approach seems to be a much more realistic way for the surveillance of quality of all pharmaceuticals, including brand and generic products.

Investing in human and economic resources for an excellent system of adverse drug reaction surveillance in a chaotic, irrational and/or bad quality drug market is simply nonsense and confounds health professionals and the public with regard to the priorities of surveillance of the whole therapeutic chain. Adverse drug reaction surveillance systems must grow in parallel with the abovementioned initiatives, as well as with measures aimed at rationalising the drug market, and providing the best pre-graduate training and postgraduate continuous education regarding rational drug prescription and use.

Acknowledgements

We acknowledge support from Departament de Sanitat i Seguretat Social, Generalitat de Catalunya.

Our thanks to Mariano Madurga (Head of the Coordinating Centre of the Spanish Pharmacovigilance System, Agencia Española del Medicamento), for his comments on the MedDRA dictionary.

References

1. The Uppsala Monitoring Centre. Adverse reaction terminology. Uppsala: The Uppsala Monitoring Centre, 1998
2. Brown EG, Wood L, Wood S. The Medical Dictionary for Regulatory Activities (MedDRA). Drug Saf 1999; 20: 109-17
3. Meyboom RHB, Lindquist M, Flygare AK, et al. The value of reporting therapeutic ineffectiveness as an adverse drug reaction. Drug Saf 2000; 23: 95-9
4. The Uppsala Monitoring Centre. Safety monitoring of medicinal products. Guidelines for setting up and running a pharmacovigilance centre. Uppsala: UMC, 2001
5. Stolley PD, Laporte J-R. The public health, the university, and pharmacoepidemiology. In: BL Strom, editor. Pharmacoepidemiology. Chichester: Wiley & Sons, 2000: 75-89
6. Charatan F. Fake prescription drugs are flooding the United States [abstract]. BMJ 2001; 322: 1443
7. Wondemagegnehu E. Counterfeit and substandard drugs in Myanmar and Viet Nam. WHO/EDM/QSM/99.3. Geneva: WHO, 1999
8. World Health Organization. Marketing authorization of pharmaceutical products with special reference to multiscore (Generic) Products. A manual for a drug regulatory authority. Regulatory Support Series, No. 5. WHO/DMP/RGS/98.5; Geneva: WHO, 1999
9. Moride Y, Haramburu F, Requejo AA, et al. Under-reporting of adverse drug reactions in general practice. Br J Clin Pharmacol 1997; 43: 177-81
10. Pécoul B, Chirac P, Trouiller P, et al. Access to essential drugs in poor countries: a lost battle? JAMA 1999; 281: 361-7
11. WHO Drug Information. The dangers of counterfeit and substandard active pharmaceutical ingredients. WHO Drug Information 1997; 11: 123-7

Correspondence and offprints: Dr *Joan-Ramon Laporte*, Fundació ICF, Universitat Autònoma de Barcelona, Hospital Vall d'Hebron, P. Vall d'Hebron 129-139, E-08035-Barcelona, Spain.
E-mail: jrl@icf.uab.es