Pharmacogenovigilance – An Idea whose Time has Come

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1. INTRODUCTION

With growing technological advances, newer and more effective drugs are being developed and used on an ever-growing scale for people with various medical conditions. Yet early detection of population signals pertaining to drug toxicity or treatment resistance has been problematic. Oftentimes, such signals are detected far too late and thus markedly risk population health. A meta-analysis published in 1998 has suggested that adverse drug reactions (ADRs) were responsible for over 100,000 deaths making them between the fourth to sixth commonest cause of death [1], not far behind the deaths caused by cancer and heart disease. ADRs have been a major clinical problem, accounting for increased length of stay in hospitals as well as being a drain on health resources [2]. Serious ADRs (SADRs) reported to the US Food and Drug Administration (FDA) from 1998 through 2005 showed marked increase (2.6-fold, from 34,966 to 89,842) and fatal ADRs increased 2.7-fold (from 5,519 to 15,107) [3].

The standard drug approval process evaluates usually no more than 3,000 patients and healthy subjects combined; the existing drug development paradigm is thus able to confirm the primary therapeutic benefits and detect only the common ADRs of new drugs. Less common ADRs (e.g., <0.1%) are typically detected after introduction of a new medication for routine clinical use. In fact, SADRs may be discovered as long as 36 years after regulatory approval [4]. Epidemiology of ADRs noted above underscores the importance of this public health problem and highlights the need for improved "early warning systems" to manage the risks of prescription drugs.

2. PHARMACOVIGILANCE

Pharmacovigilance is a concept of fundamental importance for post-marketing surveillance of pharmaceuticals (safety and efficacy) and medication incidents. Regulatory systems for post-marketing surveillance of ADRs have been established by governments in Western Europe and North America since late 1970s [5], although they still remain cursory in many parts of the developing world. Between 1997 and 2009, twenty-two licensed drugs with wide clinical use were withdrawn from the pharmaceutical market in Turkey, similar to other countries [6], due to safety

issues and public health advisory decisions by the FDA or the European Medicines Agency (EMEA). Drug-induced hepatotoxicity and QT interval prolongation account for a considerable number of these withdrawals. However, the precise number of patients who experience ADRs and the identifiable national data that lead to withdrawal decisions are often missing for many countries.

In a modern pharmacovigilance system, spontaneous reporting of ADRs is one of the key mechanisms that allow the detection of new, rare medication incidents and SADRs. However, causality assessment and ascertainment of the underlying ADR mechanisms in these reports are complicated [7]. Synthesis of ADR reports into unambiguous biological signals can be delayed due to institutional and international fragmentation of the attendant pharmacovigilance systems and regulatory standards [8]. When a genuine ADR signal is detected in a specific country, it is difficult to extrapolate such findings to other populations and geographical regions in a fast and accurate manner.

These limitations summarized above collectively raise the following question: Are there newer approaches/ technologies that can help better design pharmacovigilance systems so that drug toxicity and/or resistance signals are detected earlier, and in a more mechanistic manner to permit population level extrapolations?

3. LINKING PHARMACOVIGILANCE AND PHARMACOGENOMICS: PHARMACOGENOVIGILANCE

Pharmacogenomics is the study of variability in pharmacokinetics and pharmacodynamics in relation to human genomic variation. Pharmacogenomics has its roots in biochemical genetics and the works of Archibald Garrod (1857–1936) who suggested the chemical individuality of humans as a basis for certain inborn errors of metabolism such as alkaptonuria [9]. Both pharmacogenomics and pharmacovigilance, in essence, aim to understand "heterogeneity" and population substructure in the distribution of drug efficacy and safety signals. Despite this undeniable conceptual and practical synergy, these two disciplines and their interest groups have not converged appreciably to date. In this regard, it is notable that the drugs that are frequently cited in ADR studies (59%) are reportedly metabolized by at least one enzyme with a genetically polymorphic variant allele known to be associated with altered drug metabolism [10]. This editorial proposes the new term "**pharmacogenovigilance**", defined as pharmacovigilance activities informed and guided by accompanying pharmacogenomics analyses. Those who engaged in pharmacogenovigilance should be considered as an integral component of the healthcare teams

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charged to identify the pharmacoepidemiology signals for drug toxicity and resistance with new medications. Not surprisingly, the literature is now providing the early signposts that the time has come for pharmacovigilance to take interest in pharmacogenomics, and vice versa [11-13]. The idea of pharmacogenovigilance could conceivably be implemented concretely in the following therapeutic contexts as suggested below.

4. PUTTING PHARMACOGENOVIGILANCE INTO PRACTICE

Pharmacovigilance has long relied on spontaneous reporting of ADRs. The problem is that these spontaneous reports often do not have a mechanistic underpinning nor firm causality assessment. Pharmacogenomics analysis can help add a more mechanistic insight on these reports and contribute to causality assessments. In other words, pharmacogenovigilance would elevate the pharmacovigilance reporting to a more mechanistic context and could "raise the bar" for pharmacovigilance reporting standards, making them more scientific and mechanism oriented.

"Mechanism orientation" noted above is significant because once a mechanism of an ADR is identified using pharmacogenomics tests, it is possible to generalize a pharmacovigilance signal to other populations. If a safety signal is observed in patients who are, for example, ultrarapid metabolizers of CYP2D6, then it would logically follow that in Ethiopia where the prevalence of CYP2D6 ultrarapid metabolizers is nearly 30%, the risks and safety concerns could be even greater potentially. Suggested pharmacogenovigilance concept would help such generalizations among populations for drug ADR signals more feasible. Pharmacogenovigilance can be accomplished reactively (e.g., when a spontaneous ADR is reported) or prospectively and proactively. For new drug candidates where early phase clinical data suggest, e.g., toxicity in CYP2D6 ultrarapid metabolizers, phase 4 clinical trials can be planned and focused more on the CYP2D6 ultrarapid metabolizers. It is noteworthy that pharmacogenovigilance would also be relevant in the context of drug regulation based on conditional approval (with post-marketing continued collection of drug outcome data) [14].

National pharmacovigilance centers can develop methods for informing the health care professionals and patients about a possible pharmacogenomics involvement in the pathogenesis of a reported ADR, and facilitate access to high-throughput genomic analyses. Indeed, a pilot study in the Netherlands demonstrated the feasibility of selecting and genotyping patients based on spontaneous ADR reports [12, 13]. Recently, van Puijenbroek *et al*. [12] posed the question on whether pharmacovigilance centers could provide the appropriate clinical and scientific information needed for the decision to genotype a patient who has experienced an ADR, possibly due to a genetic variation. In this regard, the extent of participation of health professionals in genotyping their patients was reported to be relatively high (39.5%). This might allow co-reporting of both pharmacogenomics data and pharmacovigilance data in spontaneous ADR reports. Lastly, it should be noted that pharmacogenovigilance could include not only ADRs but also analysis of drug resistance and therapeutic failures.

5. CONCLUSIONS

The idea of genetic components of drug effects was proposed by Arno Motulsky in 1957 in a seminal article [15]. After more than five decades, pharmacogenetics and pharmacogenomics have now become a recognized mainstream specialty in clinical medicine and biomedical sciences. As with any maturing field, subspecialization in pharmacogenomics should be expected. This subspecialization thus far materialized along the therapeutic areas such as psychiatry, oncology and infectious diseases. This editorial proposes that other forms of subspecialization are now timely: pharmacogenovigilance is likely to bring both pharmacogenomics and pharmacoepidemiology "on line" on how best to prevent, detect and manage ADRs and drug resistance. Perhaps one of the greatest advantages of the joint study of human genomics variation and drug epidemiology signals is that it offers the possibility to move beyond descriptive summaries of ADRs (and thus allowing broader mechanism oriented extrapolations and preventive health interventions).

Pharmacovigilance cannot afford to neglect the concept of pharmacogenomics. In the near future, it might also be unethical not to use established pharmacogenomic tests that are supported by an evidence base on their analytical validity, clinical utility and cost-effectiveness. National pharmacovigilance systems firmly grounded in genomics advances are essential and could play a timely role to integrate different sources of information for assessment of casual relationships between intake of drugs and ADRs in different populations. In July 2005 Turkish Ministry of Health adopted a more systematic approach to the safety of prescription medicines and introduced new regulations for pharmacovigilance activities. In this regard, the Turkish Pharmacovigilance Center (TUFAM) aims to assess new pharmaceutical preparations for both effectiveness and safety prior to market authorization as well as during the postmarketing phase. The potential adverse effects of prescription drugs and the spontaneous reports are shared with the World Health Organization (WHO). All low and middle income countries would be advisable to establish their own activities relating to the detection, assessment, understanding and prevention of ADRs or any other possible drug-related problems like the existing national or regional systems of the developed countries. This will help to build a global SADR network and broad international cooperation with agencies such as the WHO and the Ministries of Health in both developed and developing countries. National pharmacovigilance centers should make the reporters of ADRs aware of the fact that genetic factors may play a role in the occurrence of an ADR, which can be a valuable starting point for pharmacogenomics studies.

DUALITY/CONFLICT OF INTERESTS

None declared/applicable.

ABBREVIATIONS

ADR	=	Adverse drug reactions
EMEA	=	European Medicines Agency
FDA	=	U.S. Food and Drug Administration
SADR	=	Serious adverse drug reactions
TUFAM	=	Pharmacovigilance Center of Turkey
WHO	=	World Health Organization

REFERENCES

[1]   Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients - A meta-analysis of prospective studies. JAMA 1998; 279: 1200-5.

[2]   Bates DW, Spell N, Cullen DJ, *et al*. The costs of adverse drug events in hospitalized patients. JAMA 1997; 277: 307-11.

[3]   Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. Arch Intern Med 2007; 167: 1752-9.

[4]   Ladewski LA, Belknap SM, Nebeker JR, *et al*. Dissemination of information on potentially fatal adverse drug reactions for cancer drugs from 2000 to 2002: First results from the research on adverse drug events and reports project. J Clin Oncol 2003; 21: 3859-66.

[5]   Abraham J, Lewis G. Regulating Medicines in Europe. London: Routledge 2000.

[6]   Giacomini KM, Krauss RM, Roden DM, *et al*. When good drugs go bad. Nature 2007; 446: 975-7.

[7]   Giezen TJ, Mantel-Teeuwisse AK, Leufkens HG. Pharmacovigilance of biopharmaceuticals: challenges remain. Drug Saf 2009; 32: 811-7.

[8]   Abraham J, Davis C. Discovery and management of adverse drug reactions: The nomifensine hypersensitivity syndrome, 1977-1986. Soc Hist Med 2009 [Epub ahead of print, November 5]; doi:10.1093/shm/hkp049.

[9]   Garrod AE. Incidence of alkaptonuria: A study in chemical individuality. Lancet 1902; 2: 653-6.

[10] Phillips KA, Veenstra DL, Oren E, *et al*. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. JAMA 2001; 286: 2270-9.

[11] Howland RH. Pharmacogenetics and pharmacovigilance. Drug Saf 2009; 32: 265-70.

[12] van Puijenbroek E, Conemans J, van Grootheest K. Spontaneous ADR reports as a trigger for pharmacogenetic research: a prospective observational study in the Netherlands. Drug Saf 2009; 32: 255-64.

[13] van Puijenbroek E, Conemans J, van Grootheest K. Spontaneous reports and pharmacogenetics: the role of the pharmacovigilance centre. Drug Saf 2009; 32: 357-8.

[14] Strom BL. How the US drug safety system should be changed. JAMA 2006; 295(17): 2072-5.

[15] Motulsky AG. Drug reactions, enzymes and biochemical genetics. JAMA 1957; 165: 835-7.