Review Paper

Pharmacovigilance in Developing Nations: Are We Doing Enough?

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ABSTRACT

The developed world recognized the need of an effective and efficient pharmacovigilance system after the thalidomide disaster of 1961. Once the Uppsala Monitoring Centre (UMC) was established in Uppsala, Sweden, most of the countries in Europe and the American continents became sensitive to the need of bringing all adverse effects of drugs to light. Consequently, these countries started contributing actively to the international database of adverse drug reactions.

Ironically, the developing nations of Asia and Africa, which need this system the most, have lagged far behind the developed nations in adverse event reporting, with vast ramifications. India, which joined the UMC as early as 1998, has a very insignificant contribution to this database. Less than 27% of lower middle income and low income economies have national pharmacovigilance systems registered with the WHO programme, compared with 96% of the high income countries in the Organization for Economic Co-operation and Development. Lack of an established pharmacovigilance network with a clear cut charter of duties for all concerned, lack of stringent regulatory compulsions, lack of the appropriate concern for pharmacovigilance in healthcare professionals, lack of time at all levels due to excessive patient load in all busy hospitals, lack of awareness in the general population regarding medicine and medical rights in general and adverse drug reaction (ADR) reporting in particular, are a few factors which have contributed to this unsatisfactory state of affairs.

Thus it is imperative that developing nations such as India, which are now becoming a hub of global clinical research, strictly enforce a stringent policy of pharmacovigilance and solicit active intervention of all healthcare professionals, as well as the general population, to ensure that disasters like thalidomide are restricted to the pages of pharmaceutical history.

Key Words: Pharmacovigilance; Adverse event reporting; Adverse drug reaction; Signal detection

Introduction

In 1957, a very "safe" drug, which was claimed to be harmless even in pregnant women, entered the German markets for the treatment of insomnia. Around the same time, the drug was found to be quite effective in morning sickness in pregnant ladies by an Australian obstetrician, who began using it for this "off-label" indication. In 1961, the same obstetrician began to correlate severe birth defects with this so called "harmless" compound. Neonates born to mothers who were given this drug showed *phocomelia*, or seal like limbs (flipper-limbs). Other reports also started coming in from Germany, suggesting the same problem. By March 1962, the drug was banned in almost all the countries where it was marketed. The drug was thalidomide, and the incident has gone down as the worst possible disaster in the annals of pharmaceutical history.[1]

The thalidomide tragedy shook up the European countries, while USA began felicitating one of its very alert FDA inspectors who had prevented the approval of thalidomide in that country. Frances Kelsey, a US FDA inspector, felt that the application submitted for the approval of thalidomide contained insufficient data on its safety and efficacy, particularly on transplacental

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transmission. She also felt that the results of the clinical trials of the drug in the US were not entirely reliable. Since clinical trials in US at that time did not require a mandatory FDA approval, millions of thalidomide tablets were administered to thousands of pregnant ladies even in the USA. Most importantly, none of the physicians participating in the thalidomide trials ever tracked their patients for any harmful effects, which prompted the Kefauver-Harris Drug Amendment Act in 1962, tightening the process of drug approvals and subsequent surveillance.[2] This incident can be taken as the launching pad for scientific pharmacovigilance.

Developing Nations and Pharmacovigilance

Even though the concept of pharmacovigilance was officially adopted by the world in 1963 and has shown a steady growth thereafter (**Table 1**), it continues to remain in a nascent stage in the developing nations, including India. Consequently, there is hardly any data on the pharmacovigilance services of the developing nations. It is estimated that less than 27% of lower middle income and low income economies have national pharmacovigilance systems registered with the WHO programme,[3] compared with 96% of the high income countries in the Organization for Economic Co-operation and Development.[4] The contribution of different countries towards global pharmacovigilance is shown in **Fig 1**. This falls pathetically short of the expected awareness and reporting of adverse events to drugs, since developing nations offer the best platform for clinical research.

Countries like India, with a vast diversity in ethnicity, a large treatment-naive population, English-speaking, skilled doctors, availability of ample clinical material, cost-savings and many other advantages offer optimal grounds for performing clinical trials.[5] Middle East countries, especially Israel, Turkey, Iran, and Saudi Arabia are currently involved in extensive clinical research, as per a report from the NIH, USA.[6] Other Middle East countries such as Oman, Qatar, Kuwait, Yemen, UAE, Jordan, Bahrain etc., are also expected to follow suit. Till 2007, only six sub-Saharan African countries (South Africa, Zimbabwe, Tanzania, Mozambique, Nigeria, and Ghana) were full members of the WHO Pharmacovigilance programme.[4] However, a recent article by Ambrose Isah et al states that 24 African countries are now members of the WHO programme, with a further nine countries as associate members.[7] In spite of the usual constraints faced worldwide in developing countries, the contribution of Latin America appears to be somewhat better, as per a report by Gonzalez.[8]

In order to come up with suggested solutions, it is imperative that we first understand the main reasons for this sorry state of affairs in developing nations. The major reasons (as outlined in **Fig 2**) are:

Infrastructure, regulations and compliance: Most of the developing countries lack a foolproof system of adverse event reporting. In spite of available guidelines on pharmacovigilance from the specific regulatory agency

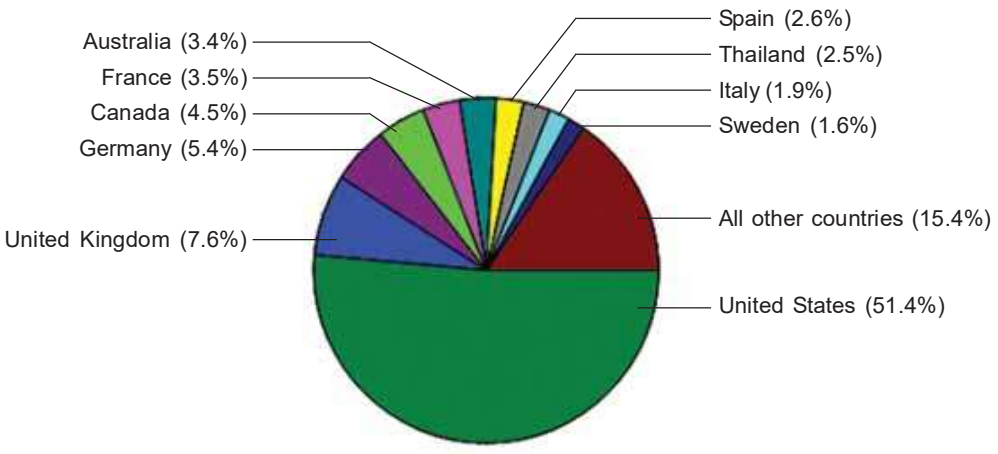

Fig 1: Percentage Distribution of the Contribution of Various Countries for Global Pharmacovigilance Graphic from the Uppsala Monitoring Centre, 2012. (*Reproduced with permission*)

of that country, compliance of the same remains unsatisfactory. There is hardly any monitoring or strict enforcement of the guidelines, leaving it to the personal preferences of the healthcare providers, contract research organizations (CROs) and pharmaceutical companies to collect and disseminate data on pharmacovigilance. Very few organizations have clear cut standard operating procedures (SOPs) and charter of duties for the respective personnel involved in pharmacovigilance. Moreover, timelines for the submission of adverse drug reaction (ADR) data in the form of periodic safety update reports (PSURs) are also not followed strictly, thereby causing delay in the recognition and reporting of adverse reactions hitherto unknown.

Lack of sensitivity and time: In all upcoming economies where the doctor-to-patient ratio is abysmal, curative medicine always takes priority over preventive medicine and pharmacoepidemiology (study of the use and effects of drugs in a large number of people). It is very difficult to sensitize an overburdened healthcare worker (HCW) to the importance of gathering drug safety data. Even if the HCW does realize the holistic importance of this task, he/she may not find time to record the details meticulously in the ADR reporting proforma. In routine practice, recording safety data is left to the lowermost HCW in the hierarchy, who is professionally under-qualified to realize the importance of the work he is doing. This also raises concerns about the authenticity and reliability of the collected data.

Lack of awareness in the general population: Awareness on health-related issues, diseases, medication and adverse effects of medication is quite low in the general population living in developing countries. Consequently, reporting of a suspected adverse event to the patient's doctor/HCW may not be done at all, or very late. This may lead to an important ADR escaping the attention of the medical fraternity completely, or being brought to light very late, when a lot of harm has already been done. Many patients tend to correlate the adverse effect to the inherent disease or pathological state, and never report the same to their doctors.

Table 1 Historical Milestones in Global Pharmacovigilance

Year	Event
1963	16th World Health Assembly adopts a resolution stressing the need for early action for rapid dissemination of information on adverse drug reactions.
1968	(a) WHO Pilot Research Project for International Drug Monitoring : To develop an international system for detecting hitherto unknown or poorly understood adverse effects of drugs. (b) WHO Programme for International Drug Monitoring : Initiation of global pharmacovigilance.
1978	Transfer of the WHO programme to the Uppsala Monitoring Centre (UMC) in Sweden : Management of an international database of adverse drug reaction reports received from participating countries – from a total of 10 countries in 1968 to 106 countries by Aug 2011.
1980s	Launch of the Programme on Drug Development and Use, with detailed recommendations, by the Council for International Organizations of Medical Sciences (CIOMS) : Provided a forum for policy makers, pharmaceutical manufacturers, government officials & academicians to make recommendations on the communication of safety information between the drug regulatory agencies & the pharmaceutical industry.
1984	International Society of Pharmacoepidemiology (ISPE) and The European Society of Pharmacovigilance (ESOP) (1992), later the International Society of Pharmacovigilance (ISoP): Formal introduction of pharmacovigilance in the research & academic arena, with increasing integration into clinical practice.
1990s	Adoption of CIOMS recommendations by the International Conference on Harmonization (ICH)
Beyond 1990s	Other countries initiate drug surveillance systems, e.g., Prescription Event Monitoring System (PEM) in New Zealand & UK, Record Linkage System in USA & Canada, and the Case Control Studies in USA
1998	India joins hands with the UMC
2005	Revised Schedule Y of the Drugs & Cosmetics Act of India 1940 : More stringent guidelines on Pharmacovigilance

Lack of resources and expertise: With limited budgeting and a perpetual deficiency of trained staff, optimal pharmacovigilance becomes quite difficult. Such circumstances mandate the adoption of unsatisfactory shortcuts for ADR reporting, with correspondingly unsatisfactory results.

Lack of communication: A suspected ADR can be consolidated by effective communication between CROs, hospitals and pharmaceutical companies involved in the research and marketing of a specific molecule. However, there is hardly any communication between these institutions due to a multitude of reasons, leading to an avoidable delay in the recognition of an ADR, as also for its entry into a common database.

Bringing Pharmacovigilance in Developing Nations up to Global Standards

The preceding sections have highlighted the fact that all the developing countries of the world are indeed not doing enough in the field of pharmacovigilance. To suggest that a common solution would serve all the affected nations would be absurd and impractical, due to specific demographic, economic and infrastructural constraints of a particular country. However, all such nations must collectively, comprehensively and willingly strive to contribute as a productive and enlightened member of the WHO pharmacovigilance programme, so also ensuring safe and evidence-based medicine amongst them.

Suggested measures which can be adopted, as per the customized requirements of individual nations include the following (**Fig 3**):

Strict enforcement of guidelines and regulations on pharmacovigilance: Regulatory agencies of individual nations must comprehensively enforce stringent regulations on the collection, collation, analysis and subsequent submission of safety related data of all new drugs and existing drugs, with appropriate punitive action against defaulters. A checklist must be maintained at all levels so that timely submission of PSURs is ensured.

Training and awareness: Awareness of adverse reactions to drugs must begin at the grass root level. Various campaigns can be organized by government agencies, NGOs, CROs, hospitals & the pharmaceutical industry to spread awareness about those diseases and their treatments with which they are specifically involved. For example, a cancer hospital and a pharmaceutical company manufacturing anti-malignancy drugs can collectively campaign for creating awareness on cancer, its treatment and the expected adverse effects of such drugs, especially drugs in phase III clinical trials and in the post-marketing surveillance (PMS) phase. More importantly, spontaneous reporting (notification of suspected adverse reaction to drugs by healthcare professionals/patients/their relatives etc., directly to the regulatory agencies or to the company marketing the product) and signal detection (detection of a new pattern or trend of adverse reactions or seemingly significant new findings in the safety database) must be known to all the concerned staff, as also to the patient who is receiving a new drug under PMS. Similarly, causality assessment of suspected ADRs must be done meticulously, so that a new suspected ADR can be attributed to that particular drug with an acceptable degree of confidence. All of this is possible only by

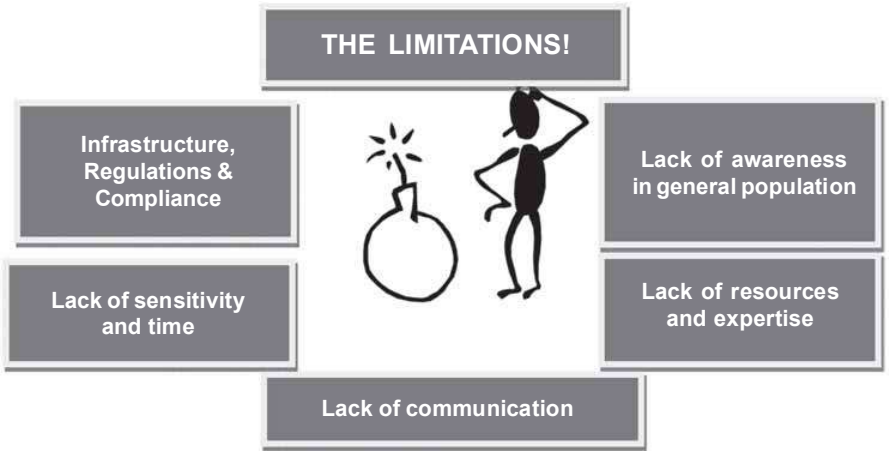

Fig 2: The Problems

adequate and effective training of all the concerned staff. Appropriate incentives may be given to encourage voluntary and sincere efforts in the collection of safety data from the HCWs. This is more pertinent to countries with very high population densities like India, where the entire medical and para-medical staff is overburdened.

Optimization of resources and expertise: Regulatory agencies as well as related government organizations should synchronize the central pharmacovigilance activities with those of the peripheral centers, so that safety data collection is never compromised at any level. There should be an effective two-way liaison between data collecting, analyzing and submission agencies so that resources can be pooled and data can be collected and analyzed correctly and appropriately. Pooling of resources is of particular value between government and private institutions, where a mutually beneficial relationship can be created.

Effective communication and collaboration: Collaboration must be encouraged amongst individual academic investigators, CROs, drug companies, private hospitals and government agencies to develop common adverse reaction reporting forms, so as to generate a common database. The administrative rights of the central database can be given to a sufficiently large organization competent enough to take over this task, by mutual consent of the participating agencies and the regulatory authority. In addition, cross communication must be encouraged between organizations researching upon, or marketing common molecules, so that suspected adverse effects can be reliably assessed for causality. Examples of effective collaborations between organizers of public health, drug researchers/campaigners and regional surveillance systems are available in Africa, such as the East African network for monitoring antimalarial treatment[9] and the network for assessing health and demography in developing countries.[10]

Role of the pharmaceutical industry: In all developing nations, the pharmaceutical industry has the potential of playing a very major role in pharmacovigilance related activities, which is much beyond the usual compulsions of obtaining a marketing license (Marketing Authorization Holder – MAH). A public-private partnership in the PMS phase can effectively demonstrate the actual efficacy and safety of the drug in the real world situation, as was the case with indigenously manufactured tenecteplase and its use in STEMI patients in India.[11] Moreover, the large trained manpower available with reputed pharmaceutical companies can be effectively harnessed in not only the actual data collection, but also indirectly, in the training and awareness of the general population to participate in spontaneous reporting of ADRs, through various hospitals and polyclinics using their products. The pharmaceutical industry can also utilize the print and electronic media for such activities.

Global and government funding: The onus of ensuring optimal, efficient and timely ADR reporting at the international level falls on the WHO and the UMC. The WHO needs to initiate a method of funding

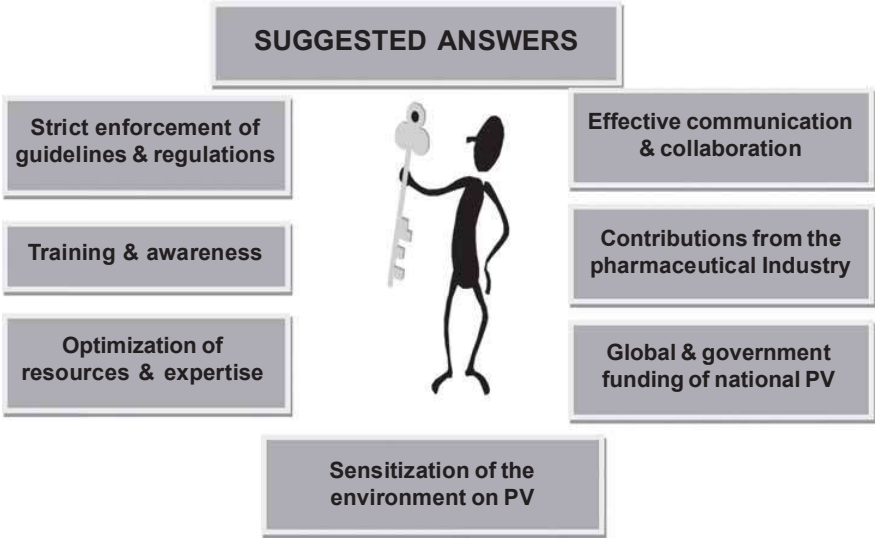

Fig 3: Suggested Solutions

pharmacovigilance activities in the developing countries, in liaison with the major stakeholders in global drug research. On similar lines, governments of all such nations should also partially subsidize these activities, either directly or in conjunction with major pharmaceutical companies, so that lack of resources and funds are no more an excuse for ignoring ADR reporting.

Sensitization of the environment: Last but not the least, sensitization of the environment towards ADR reporting is a collective responsibility of the drug regulatory agencies, the entire healthcare fraternity and the pharmaceutical industry. This would need a pro-active approach from all the concerned agencies, which will have to collectively decide the modalities of execution to eliminate an all pervading lackadaisical attitude. Interestingly, ADR reporting not only cautions the world against the adverse effects of the drugs, but also gives valuable inputs on cashing upon these unexpected effects, as was the case with minoxidil [hypertrichosis being utilized for alopecia (male pattern baldness)] and cyproheptadine (appetite stimulating effect being utilized to increase the appetite of young children).

Conclusion

The importance of pharmacovigilance as a tool for optimization of modern evidence-based medicine cannot be over-emphasized. Even though the developed world has adopted this concept to a satisfactory extent, developing countries in Asia, Africa and Latin America are still lagging behind, due to a variety of reasons, especially lack of adequate regulatory control, awareness and willpower. However, this limitation needs to be resolved on an urgent basis with the regulatory agencies at the helm of affairs. Strict enforcement of practical pharmacovigilance, adequate training, sensitization of the environment, and encouraging active participation of the pharmaceutical industry as well as the general population are a few suggested measures which may help to bring the concept of pharmacovigilance up to global standards in these countries. Time is indeed at premium; the sooner the affected nations respond to this wake up call, the better.

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