Drug Safety 2005; 28 (7): 647-650
0114-5916/05/0007-0647/$34.95/0

The Pharmacovigilance System in India

Pharmacovigilance has been defined as the science of activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

The concept of adverse drug reactions (ADRs) is not new in India. The Charak Samhita, a text on Ayurvedic medicine, a traditional Indian system of medicine dating back to the 7th century BC, described physicians, medicine, pharmacists/nurses and patients as factors that determine the success or failure of treatments. Furthermore, it cautioned that poorly understood and improperly administered drugs are like poisons.

Later, in 500 AD, Vagbatta (an Ayurvedic physician) described contraindications, adverse events and their management. He stated that a "drug which alleviates symptoms but causes another disease [iatrogenic] sooner or later is not appropriate"; thus, he had identified the possibility of delayed adverse effects of drugs and emphasised the importance of rational drug use.[1]

Published literature reports of ADRs from India are found in the history of modern medicine. A search in PubMed that used the keywords 'India' and 'adverse drug reaction' located 1030 articles compared with a total of 20 588 publications from India.

However, it was not until 1986 that a formal ADR monitoring system consisting of 12 regional centres, each covering a population of 50 million, was proposed for India.[2] The healthcare system in India consists of three tiers: tertiary teaching hospitals, secondary district hospitals and primary health centres. It was proposed that five primary health centres, each catering for 0.1 million people, would provide information to one district hospital and that ten such district hospitals would provide data to each regional centre located in a teaching hospital.

The objectives of the ADR system in India were then envisaged to be as follows.

- Collection of information for old drugs on all serious and previously unreported ADRs with a view to quantifying the incidence and identifying risk factors.
- Development of methods to establish causality and to predict (prevent) ADRs.
- Validation of data and identification of regional variation.
- Identification of ADRs to new drugs through spontaneous reporting.

In 1989, under the aegis of the Drug Controller of India, six regional centres were set up in Mumbai, New Delhi, Calcutta, Lucknow, Pondicherry and Chandigarh. These centres were located in teaching hospitals and provision for staff was made.[3]

In 1997, following an international meeting in Mumbai, India joined the WHO Programme for International Drug Monitoring managed by the Uppsala Monitoring Centre. The centre in New Delhi was identified as the national centre, while the centre in Mumbai was identified as the WHO special centre.

Of the six centres, only the centres in Mumbai and New Delhi were active. The centre in New Delhi started a newsletter and the centre in Mumbai prepared a spontaneous reporting form that was published in professional journals. The emphasis was on intensive hospital monitoring and investigating specific drug-related issues. The response to spontaneous reporting appeals was poor. However, the centre in Mumbai then developed a postal survey system to address specific drug-related problems.[4] A postal survey was carried out to assess ADRs to ciprofloxacin that, although contraindicated in children, was used in children with chloramphenicol-resistant typhoid. Data was obtained for 3000 children and follow-up revealed the existence of acute adverse effects (arthropathy) and the absence of delayed effects.[5,6]

The same method was successfully used for getting information on other drugs, e.g. mefloquine. Further adverse events due to interaction between Ayurvedic drugs and modern drugs,[7,8] and ADRs to adulterated drugs were identified.[9] Intensive hospital monitoring identified hepatotoxicity due to antitubercular drugs and Stevens Johnson Syndrome as being the most common serious ADRs.[10]

India has contributed to the WHO global safety database and has further benefited by having access to the WHO database. For regulatory decision-making processes, data on ADRs and information

on the regulatory status of specific drugs in other countries became available.

Despite these achievements and contributions, it was well recognised that the ADR system in India was functioning below its optimum level. The ADR monitoring centres were considered *ad hoc* and, therefore, appropriate levels of funding were not made available, which put severe constraints on staff appointment and motivation.

The current patent laws in India have permitted the Indian pharmaceutical industry to synthesise and market drugs that have already been extensively marketed elsewhere in the world. Thus, the public health system in India has mostly administered well known drugs for the control and prevention of diseases. Much is already known about the safety profiles of many of these drugs and, therefore, it was perceived that there was no real need for ADR monitoring. There was apathy on the part of physicians, pharmacologists and patients towards ADR reporting.

However, recent changes in the pharmaceutical industry and expected changes in both patent law and the Drugs and Cosmetic Act mean that new drugs will be developed in India and that new drugs that are developed elsewhere, but are not yet marketed, will be tested in India. Thus, drugs about which we only have limited safety information will become available for use. In addition, several donor agencies are coming forward to provide new drugs to be used in public health and new drugs and combinations are being developed for tropical diseases such as malaria and leishmaniasis. Recently, the WHO and UNAIDS have undertaken an international effort to have 3 million people in resource-limited countries on antiretroviral therapy (ART) by the end of 2005.[11]

All these changes will increase the population's exposure to drugs. There will be benefits; however, there will be a need to monitor risks. Information on ADRs will need to be collected, systematically processed, integrated and managed. Important safety signals and new safety hazards will need to be identified. The Indian regulatory agency will need to react to safety issues in a timely manner, providing information to doctors, making appropriate changes to package inserts, imposing restrictions on use and possibly withdrawing agents from the market.

As well as these changes within India, the scope of pharmacovigilance has broadened from providing data for regulatory decisions to being a science that plays a major role in clinical practice and the development of public health policy.[12] Recognising the need for improved ADR monitoring in India and in consultation with the pharmacovigilance centres in the India, the Indian Government sent a proposal to the World Bank for funding. It was recognised that in order to capture data from various parts of a country the size of India, interpret it and make decisions, the involvement of academic institutions and medical colleges that are spread out all over the country would be extremely useful. The World Bank has approved the proposal with an annual grant of $US0.1 million for 5 years. The new pharmacovigilance system was launched in November 2004.

The project will be coordinated by the pharmacovigilance unit at the Central Drugs Standard Control Organisation under the Director General of Health Services for the Government of India. The unit will be guided by a National Pharmacovigilance Advisory Committee that will recommend procedures and guidelines for regulatory interventions. Two zonal pharmacovigilance centres (New Delhi for the North-East, Mumbai for the South-West) will coordinate the nationwide programme. Four regional pharmacovigilance centres have been identified across the country. Peripheral pharmacovigilance centres in at least one teaching hospital in each state and union territory, leading medical institutions, clinics or pharmacies will be established.

The pharmacovigilance unit will receive information from the centres, review periodic safety update reports, maintain contact with international regulatory bodies, recommend regulatory actions and provide information to end users.

The national centres functioning under the WHO Programme for International Drug Monitoring are expected to play an increasingly important role in clinical practices, public health policies and regulatory decisions. Indicators of performance of the ADR centres should reflect objectives, activities and expectations. In the new pharmacovigilance system in India, each peripheral ADR monitoring centre has been given the goal of reporting 30 spontaneous reports per month. The performance of the system

could be assessed by the number of product label amendments and product withdrawals recommended.

However, the number of spontaneous reports is not a good indicator as more reports may indicate better performance of the centre or may indicate more ADRs occurring and, therefore, the failure of the pharmacovigilance system. Similarly, regulatory decisions to withdraw a drug, restrict its use or change its package insert may indicate success of the pharmacovigilance programme, but may indicate poor performance of the regulatory system in permitting the initial marketing of unsafe drugs.

The overall purpose of pharmacovigilance is improvement in the safety of medicine. Pharmacovigilance indicators to assess the performance and impact of the pharmacovigilance system need to be developed. Indicators such as the number of serious ADRs that are prevented, the number of patients counselled, number of physicians trained and costs due to ADRs that are saved, need to be developed to evaluate and assess the impact of the pharmacovigilance system and thus justify expenditure on pharmacovigilance in low resource countries such as India and other developing countries.

Nilima Kshirsagar
Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, Parel, Mumbai, India

References

1. Shrikantha Murthy KR. Vagbhata's Ashtang Hrdayam. Varanasi: Krishnadas Academy, 1998
2. Kulkarni RD. Reporting system for rare side effects of non-narcotic analgesics in India: problems and opportunities. Med Toxicol 1986; 1 Suppl. 1: 110-3
3. Kshirsagar NA, Karande SC, Potkar CN. ADR monitoring in India. In: Kshirsagar NA, Gupta KC, editors. Selected topics in clinical pharmacology. Mumbai: Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, 1990: 60-64
4. Gogtay NJ, Mangalvedhekar SS, Kshirsagar NA. Adverse drug reaction (ADR) monitoring in India and the postal survey as a useful tool for ADR detection. Pharmacoepidemiol Drug Saf 2000; 9: 235-6
5. Karande SC, Kshirsagar NA. Adverse drug reaction monitoring of ciprofloxacin in pediatric practice. Indian Pediatr 1992; 29: 181-8
6. Karande SC, Kshirsagar NA. Ciprofloxacin use: acute arthropathy and long-term follow up. Indian Pediatr 1996; 33: 910-6
7. Kshirsagar NA, Dalvi SS, Joshi MV. Phenytoin and Ayurvedic preparation: clinically important interactions in epileptic patients. J Assoc Physicians India 1998; 42: 527-33
8. Dandekar UP, Chandra RS, Dalvi SS, et al. Analysis of a clinically important interaction between phenytoin and Shankhapusphpi, an Ayurvedic preparation. J Ethnopharmacol 1992; 35: 285-8
9. Dhumal SG, Tillu RA, Gogtay NJ, et al. Suspected atropine toxicity due to contaminated metronidazole bottle. J Assoc Physicians India 1997; 45: 381-2
10. Kshirsagar NA, Karande SC, Potkar CN. A prospective survey of drug induced hepatotoxicity in a large hospital. Indian J Gasteroenterol 1992; 11: 13-5
11. Technical and operational recommendations to achieve '3 by 5'. Draft report from the WHO/UNAIDS Zambia consultation, 2003 Nov 18-21, Lusaka, Zambia. Geneva: World Health Organization, 2004
12. The importance of pharmacovigilance: safety monitoring of medicinal products. Geneva: World Health Organization, 2002