Adverse drug reaction monitoring

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During the course of treatment or after, some drugs prescribed to patients produce certain effects other than those desired or expected. These adverse effects cause concern both to the physician and the patient, adding to the spiralling costs of medical treatment, morbidity and mortality. They rank between the fourth and sixth leading cause of death. The science of and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problems is called pharmacovigilance, as defined by the World Health Organization. This article provides information on some recent label changes of drugs, withdrawals from the market and standard methods of adverse drug reaction (ADR) monitoring with examples. It also gives some practical details about the reporting system of ADRs in India and its applications.

Keywords: Adverse drug reaction monitoring, pharmacovigilance, drug safety.

IN November 2010, the US Food and Drug Administration (FDA) withdrew propoxyphene, sold under the brand names Darvon and Darvocet by Xanodyne Pharmaceuticals, from the market. Propoxyphene is an opioid medication that was used to treat mild to moderate pain. It has been marketed in the United States since 1976, and was withdrawn after 34 years because clinical data showed that the drug puts patients at risk of potentially serious or even fatal heart rhythm abnormalities. An estimated 10 million patients have used these products[1]. Such cases justify the necessity for monitoring new as well as old drugs in the market.

These events occur because the premarketing trials frequently have insufficient capability to reliably detect important adverse drug reactions (ADRs), which may occur at rates of 1 in 10,000 or fewer drug exposures. The trials also lack the necessary follow-up to detect ADRs widely separated in time from the original use of the drug or delayed consequences associated with long-term drug administration. They often do not include special populations such as pregnant woman or children who may be at risk of unique ADRs or of an increased frequency of ADRs compared with the general population[2]. ADRs still constitute the sixth leading cause of death in the US, after heart disease, cancer, stroke, pulmonary disease and accidents[3].

The realization that it was essential to have some form of regulation of the sale and supply of medicines has evolved slowly, with discussions starting at the beginning of the 20th century. In 1914 in the UK, the Committee on Patent Medicines gave a detailed proposal for the establishment of a formal regulatory mechanism, but this did not take effect until the thalidomide disaster in 1961. The Committee on Safety of Drugs was initiated under the chairmanship of Derrick Dunlop who started the yellow card system – a method of spontaneous reporting of ADRs. This was the start of organized systems of such reporting in Europe[4]. Now, spontaneous reporting systems have been well established throughout the world.

The aims of ADR monitoring involve detecting unknown safety problems at earlier stage and increases in their frequencies, identifying and quantifying risk factors, and preventing patients from being affected unnecessarily. The data on ADRs can be used to formulate therapeutic guidelines, take public health policy decisions, and in pharmaco-economics. Based on these facts, regulatory authorities can change package inserts, restrict the use of drugs or withdraw drugs[5]. Some examples of restricted use of drugs by the US FDA[5] are given in Table 1.

In 2011, the US FDA changed the labels, that is, the package inserts of some drugs[5]. Important label changes are given in Table 2. Physicians should be aware of these modifications before starting the drugs.

On the basis of information compiled from national as well as international trials and reports, some drugs were banned in India in 2011 (ref. 6). This list is given in Table 3.

ADR monitoring involves: (i) collecting the ADR data, (ii) assessing the causality between drugs and suspected reactions, and (iii) reporting ADRs to pharmacovigilance centres/ADR regulating authorities.

Collecting data on adverse drug reactions

A number of methods are employed to identify previously unknown detrimental outcomes attributable to the use of

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Table 1. Restricted use of drugs by the US FDA

Drug	Date	Type of restricted use	Reason
Salmetorol, formeterol (LABA)	February 2010	First line and single use is contraindicated in asthma patients.	Worsening of asthma and death.
Tramadol	May 2010	Should not be given to patients with previous histories of emotional disturbances, suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol and other central nervous system (CNS)-active drugs.	CNS depression, respiratory depression and death.
Paracetamol (acetaminophen)	January 2011	Use of paracetamol above a dose of 325 mg in combination with other analgesics is not allowed.	Risk of liver injury.
Simvastatin 80 mg	June 2011	For cholesterol reduction, high dose of 80 mg/day is not recommended.	Increased risk of muscle injury and rhabdomyolysis, which leads to kidney failure.

Table 2. Label/pack insert modifications by the US FDA

Drug	Date	Label/ pack insert modification
Paracetamol	January 2011	A boxed warning highlighting the potential for severe liver injury and a warning on the potential for allergic reactions (e.g. swelling of the face, mouth and throat; difficulty in breathing; itching, or rashes).
Antipsychotic drugs	February 2011	Treatment during pregnancy poses a potential risk to newborns. They cause extrapyramidal signs and withdrawal symptoms, including agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty in breathing and difficulty in feeding.
Proton pump inhibitor drugs, e.g. omeprazole, esomeprazole	February 2011	Used for treatment of acidity, stomach and intestinal ulcers. They cause low serum magnesium levels (hypomagnesemia) if taken for prolonged periods (in most cases, longer than one year), which in turn can result in muscle spasms (tetany), irregular heartbeats (arrhythmias) and convulsions (seizures).
Birth control pills containing drospirenone	May 2011	Possible increased risk of blood clots, the symptoms of which include persistent leg pain, severe chest pain or sudden shortness of breath.

medications. The initial step of identifying ADRs can be performed actively or passively.

Active surveillance includes reviewing medical records or interviewing patients and/or physicians in a sample of healthcare centres called sentinel sites. In data event monitoring, patients may be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or the patient at specified intervals to obtain information. Active surveillance can also be done with the help of registries. A registry is a list of patients presenting similar characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). The two registries, which differ only in the type of patient data, can collect a battery of prospective information using standardized questionnaires; for example, pregnancy exposure registries for products that are likely to be used during pregnancy[7]. Another method of ADR monitoring is through clinicians; for example, requesting them for a feedback (for a certain period of time) after the introduction of a new drug in the market or in hospital settings.

The passive methods comprise spontaneous reports and case series of similar reports. A spontaneous report is an unsolicited communication by healthcare professionals (doctors, including dentists, nurses and pharmacists) to a company, regulatory authority or an organization (e.g. WHO regional centres, poison control centres) that describes one or more ADRs in a patient who was given one or more medicinal products. This report is not derived from a study or any organized data-collection scheme. The data accompanying spontaneous reports are often incomplete. But these reports play a major role in the identification of safety signals once a drug is marketed. For instance, temafloxacin, a fluoroquinolone antibiotic, was withdrawn within six months of its introduction because of the association between its use and haemolytic anaemia in otherwise healthy individuals. Spontaneous reporting rapidly identified this ADR because it was rare in the general population and occurred within one week of drug use. Another example is that of phentermine and fenfluramine. The association between valvular heart disease in younger women and the use of these appetite suppressants took longer to identify with

Table 3. Drugs banned in India in 2011

Drug	Reasons for withdrawal in India
Cisapride	Risk of cardiac arrhythmias.
Phenylpropanolamine	Risk of stroke.
Nimesulide (below the age of 13 years)	Life-threatening hepatotoxic effects.
Sibutramine	Increased cardiovascular risk.
Gatifloxacin	High risk of developing serious hyperglycaemia (high blood sugar) or severe diabetes. It can also be responsible for liver damage, purpura and hallucinations.
Tegaserod	Increased risks of heart attack or stroke.

spontaneous reporting probably because the development of ADR required a longer period of use[2].

Epidemiologic methods can also be used in the evaluation of adverse events. These include cross-sectional study, case-control study and cohort study. In a cross-sectional study (survey), data are collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status, whereas in a case-control study cases of a disease (or event) are identified. Controls, that is, patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The other method is the cohort study in which a population at risk of the disease (or event) is followed over time for the occurrence of the disease (or event). For instance, a cohort study showed the association between rofecoxib and cardiovascular events, which led to further trials and withdrawal of this drug from the market[8,9].

When significant risks are identified in pre-approval clinical trials, further clinical studies may be called for to evaluate the mechanism of action in adverse reactions. This includes pharmacokinetic, pharmacodynamic and pharmacogenetic studies. A descriptive study design is helpful in collecting ADR information. Studies are conducted on patients with the disease and distribution of the disease in selected populations. It also includes drug utilization studies that describe how a drug is marketed, prescribed and used in a population, and how these factors influence outcomes – clinical, social and economic. These methods of collection of ADR data are described in the US FDA guidance documents[10].

Assessing causality between drugs and suspected reactions

To establish the relationship between a drug and adverse reaction(s), causality assessment is important. There is no gold standard for this assessment. Some of the widely used algorithms and scales include Naranjo's scale, WHO probability scale, European ABO system, Kramer's scale, Bayesian system, Karch and Lasagna scale, and French imputation method[7]. The categorization of causal relationships between a drug and the suspected adverse reactions varies with the scale adopted. The WHO scale categorizes the causality relationships into certain, probable, possible, unassessible/unclassifiable, unlikely, and conditional/unclassifiable, whereas the Naranjo scale categorizes them as definite, probable, possible or unlikely. In general, the following four aspects are to be considered while attributing a clinical adverse event to a drug[11]: (i) temporal time relationship between the suspected reaction and the drug; (ii) dechallenge (cessation of drug); (iii) rechallenge (reintroduction of drug), and (iv) likelihood of other possible causes.

Reporting adverse drug reactions

The National Pharmacovigilance Programme (NPP)[12] encourages the reporting of all suspected drug-related adverse events, including those suspected to have been caused by herbal, traditional and alternative remedies. Notifying seemingly insignificant or common adverse reactions would be important as it may highlight widespread prescribing problems. The programme particularly solicits reports of: (i) all adverse events suspected to have been caused by new drugs and 'drugs of current interest'; (ii) all suspected drug interactions and (iii) reactions to any other drugs that are suspected of significantly affecting a patient's management, including death, life-threatening conditions (risk of death), hospitalization (initial or prolonged), disability (significant, persistent or permanent) and congenital anomaly. Here intervention is required to prevent permanent impairment or damage.

The time-frame for reporting fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) is not later than seven days after the sponsor had information that the case fulfilled the necessary criteria; any follow-up information is to be provided within a further period of eight days. All other SUSARs are to be notified not later than fifteen days.

The various ADR regulatory authorities are: Committee on Safety of Medicine, Adverse Drug Reactions Advisory Committee, MedWatch and Vaccine Adverse Event Reporting System. The WHO–Uppsala Monitoring Committee (UMC) international database in Sweden maintains all information on ADRs. In India, NPP

comprises one National Pharmacovigilance Centre located at the Central Drugs Standard Control Organization (CDSCO), in New Delhi, two zonal centres (All India Institute of Medical Sciences, New Delhi for north and east, and King Edward Memorial Hospital, Mumbai for south and west), five regional centres (Department of Pharmacology, JIPMER Pondicherry, TN Medical College, Mumbai, IGMC Nagpur, Lady Harding Medical College, New Delhi and NRS Medical College, Kolkata) and 24 peripheral centres (including some medical colleges and hospitals approved by the Medical Council of India, private hospitals, public health programmes and autonomous institutes). The ADR form is available at any pharmacovigilance centre (see http://www.cdsco.nic.in for more details). The completed form should be sent to the peripheral pharmacovigilance centre or in case of doubts, it can be sent directly to CDSCO. The information provided is handled in strict confidence. The peripheral centre forwards the submitted form to the regional centre where causality analysis is carried out, after which it is sent to the zonal centre. The data are statistically analysed and forwarded to WHO–UMC[12].

In India, the pharmacovigilance programme is facing difficulties. Drugs are sold without prescriptions in many medical shops; hence it is difficult to trace the use of these medicines. Several preparations containing allopathic drugs are sold as herbal medicines. Also, the pharmacovigilance centres are in shortage of money as well as staff. Many doctors are reluctant about pharmacovigilance. Given below are some suggestions to address these problems: (i) awareness programmes, symposia and workshops for practitioners and healthcare workers should be arranged; (ii) the syllabus for doctors, pharmacists and nurses can be modified to make them aware of this issue; (iii) the national programme should involve the pharmaceutical industry; (iv) the policy on periodic safety update reports should be strictly implemented and (v) in hospitals ADR drop-boxes in wards, daily enquiries, e-mail alerts and thank-you letters can increase the chances of reporting. Such procedures can increase the knowledge of ADRs, and decrease the mortality and morbidity of millions of people in India.

1. Xanodyne agrees to withdraw propoxyphene from the US market. FDA news release dated 19 November 2010; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm234350.htm
2. Brewer, T. and Colditz, G. A., Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA*, 1999, **281**, 824–829.
3. Lazarou, J., Pomeranz, B. H. and Corey, P. N., Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*, 1998, **279**(15), 1200–1205.
4. Mann, R. D., *Clinical Research Manual*, Euromed Publication, UK, 2005, 2nd edn, p. 8.2.
5. MedWatch: The FDA Safety Information and Adverse Event Reporting Program; http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm
6. Drugs prohibited vide Gazette notifications dated 16 March 2011 (G.S.R. 218(E)) and 10 February 2011 (G.S.R. 82(E)); http://www.cdsco.nic.in/
7. Dellicour, S., ter Kuile, F. O. and Stergachis, A., Pregnancy exposure registries for assessing antimalarial drug safety in pregnancy in malaria-endemic countries. *PLoS Med.*, 2008, **5**(9), e187.
8. Ray, W. A., Stein, C. M., Daugherty, J. R., Hall, K., Arbogast, P. G. and Griffin, M. R., COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet*, 2002, **360**, 1071–1073.
9. Arellano, F. M., The withdrawal of rofecoxib. *Pharmacoepidemiol. Drug Saf.*, 2005, **14**, 213–217.
10. International Conference on Harmonization Guidance – E2E Pharmacovigilance Planning, 2005. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073107.pdf
11. Agbabiaka, T. B., Savović, J. and Ernst, E., Methods for causality assessment of adverse drug reactions: a systematic review. *Drug Saf.*, 2008, **31**(1), 21–37.
12. Pharmacovigilance Programme of India for Assuring Drug Safety; http://www.cdsco.nic.in/pharmacovigilance.htm

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