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Pleasures and pains of running a pharmacovigilance center

R.K. Dikshit, Chetna Desai, M.K. Desai

Introduction

“Pharmacovigilance is the science and activity relating the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.” [1] India is the fourth largest producer of pharmaceuticals in the world and an important consumer of medicines too. Each day, new drugs are introduced and prescribed. There has, however, been a lack of sound system of pharmacovigilance in India. This is in spite of the efforts made by Indian Council of Medical Research (ICMR) that established a multicentric reporting system in 1989 and a Taskforce Project in 1992. The World Health Organization (WHO) also established working relationship with two centers in India for collaborating with its Adverse Drug Reaction Monitoring Program in 1997. “National Pharmacovigilance Center” and Society for Pharmacovigilance, India (SOPI) were designated in 1998. More recently the Central Drug Standard Control Organization (CDSCO), has initiated a nationwide pharmacovigilance program under the aegis of Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare, Government of India. This program is largely based on the recommendations made by the WHO in its document titled “Safety Monitoring of Medicinal Products - Guidelines for Setting up and Running a Pharmacovigilance Center”. A nationwide network with 25 peripheral centers, 5 regional centers, and 2 zonal centers was established, in a hierarchical fashion, with predefined tasks and responsibilities allocated at each level.[2]

The National Pharmacovigilance Center

The National Pharmacovigilance Center coordinates the National Pharmacovigilance Program (NPVP). It operates under the supervision of the National Pharmacovigilance Advisory Committee. It undertakes the following tasks:

1. Monitoring adverse drug reactions (ADR) by collation, review, and evaluation of spontaneous adverse drug reaction reports received from various centers.
2. Fostering the culture of ADR notification and to generate a broad-based ADR data on Indian population and share it globally.
3. Reviewing periodic safety update reports submitted by the pharmaceutical companies. These are expected to be submitted every 6 months for the first two years of marketing in India and annually for the next two years.
4. Maintaining contacts with international regulatory bodies working in pharmacovigilance and exchange information on drug safety.
5. Assessing the regulatory information and recommending product label modifications, product withdrawals, or suspensions.
6. Providing information to end users through media.

The Department of Pharmacology, B. J. Medical College, Ahmedabad, was recognized as one of the 25 peripheral pharmacovigilance centers all over India. It is one of the five peripheral centers in western India and one of the two centers in Gujarat.

The Department of Pharmacology, B. J. Medical College, Ahmedabad had been carrying out projects on pharmacovigilance since 1992. Monitoring of adverse drug reaction in public and private hospitals in Ahmedabad was undertaken during the years 1992-2000. Several case reports and review articles in scientific journals were published on this subject. Hence the concept of pharmacovigilance and ADR reporting was disseminated to the prescribers since then, albeit in an unorganized and sporadic manner.

The Peripheral Reporting Center was sanctioned in May 2005; Dr. R. K. Dikshit was appointed its Coordinator. The Terms of Reference (TOR) were signed in August 2005. The tasks envisaged for the peripheral centers include collecting and collating at least 30 adverse drug reaction notifications every month; which are then forwarded to the respective regional center. The center is also required to carry out special projects on drug safety on request of the CDSCO, carry out causality analysis of all the ADR on a monthly basis and maintain a log of all ADR forms and notifications.

It also has the responsibility of inculcating and fostering a reporting culture among the health professionals. This is possible in several ways such as acknowledging the cooperation of the participating clinicians, providing relevant feedback, organizing training, and other scientific programs related to pharmacovigilance.
Organization of Peripheral Reporting Center, B. J. Medical College, Ahmedabad

The planning and initial groundwork began in May 2005 with a few cautious and hesitant steps, with apprehensions about the response from the clinicians and other health personnel. Having faced the practical problems with spontaneous reporting in the past, this apprehension was not totally unfounded. Clinicians never seemed to have time for reporting, the outpatient departments are too crowded to offer any time/space for our persevering motivators who pursue this cause with passion. The solace and consolation was that most pharmacologists who we met in Gujarat and elsewhere had a similar experience to narrate. The bright side of the experience was that the word about adverse drug reactions and pharmacovigilance had spread in the “prescriber” community. ADRs and ADR reporting were now being looked upon not with too much of awe, suspicion, and apprehension, but something that could be tackled and needed to be reported. And better still, pharmacologists like us were now more welcome than ever. We thus, had to proceed to an environment of strengthened trust, active participation and advocacy.

The first set of ADRs for the months of June and July 2005 was submitted in August 2005.

One of the requirements for the peripheral reporting centers under the NPVP is submission of at least 30 ADR reports each month. The peripheral reporting center - B. J. Medical College, Ahmedabad has been able to meet this target so far. Interested and motivated staff members and postgraduates of the department were initially briefed about the center and the NPVP. Then began the phase of networking with clinicians, from the Civil Hospital Ahmedabad, to begin with and later with private practitioners from the city. Interested and motivated clinicians were identified, contacted personally, and through formal meetings. They were briefed about the aims and objectives of the program and the proposed functions of the Peripheral Center. The clinicians were encouraged to report ADRs by:

- Submitting the ADR reporting forms to the center
- Notifying the ADR to the Department of Pharmacology either telephonically or in person.
- Since there are multiple specialties and clinical units involved, individual staff members/residents were allotted the responsibility of individual unit/clinical department. This ensured that all ADR notifications were promptly attended. The postgraduates also visited the outpatient departments and the wards of the participating departments to collect details of the reported cases.
- Residents from clinical departments were also encouraged to report ADRs.
- The private practitioners of the city were either contacted personally or through announcements in the meetings and newsletters of local medical associations. Brief lectures of about 10-15 min were delivered at monthly meetings of local Medical Associations.
- Posters provided by the CDSCO and other contact details were displayed prominently in the hospital premises and the offices of the local medical associations.
- Information about ADR reporting and pharmacovigilance was also disseminated to other health personnel.

- ADR reporting for special groups of drugs like ART and all other drugs used in HIV infections, anti-tubercular drugs analogics and antiepileptics was also undertaken.
- Lately efforts are also being made to reach out to areas outside Ahmedabad. One such center is at Bhavnagar where a scientific meeting was held in coordination with the local Branch of the Indian Medical Association and the Government Medical College. Efforts are on to initiate the ADR monitoring in participation with the Department of Pharmacology.

Adverse Drug Reactions Reported by the Center

The Peripheral Center has been able to meet the targets laid down under the NPVP. Most notifications were received from the departments of medicine, dermatology, psychiatry, T.B. and Chest diseases, pediatrics, ophthalmology, and surgery. Some cases were reported by private practitioners too. While the reports were forwarded to the Regional Center at Mumbai, our center too is creating a database of the ADRs reported and classifying the information based on age and gender of the patients, source of the ADR reports, causal groups of drugs, route of administration of suspected drugs, nature and clinical presentation of the adverse event, and the outcome.

Following are the salient features of the ADRs reported by our center till date:

- A total of 1048 cases of ADEs have been reported in a period of 33 months; an average of 31.7 reports per month.
- A detailed analysis of the 923 cases showed that ADRs were reported more frequently in males than in females (M:F = 1.29).
- Highest number of cases are reported in the age groups of 16-30 and 31-50 years.
- The common causal groups of drugs in decreasing order of occurrence are: antimicrobials (433), NSAIDS (100), antiepileptics (66), antipsychotics (57), antihypertensives (35), corticosteroids (31), anticholinergics (26), antiemetics (19), antidepressants (17), antidiabetics (15), and over the counter (OTC) medicines (20).
- The common reactions observed are skin rashes (149), itching (94), vomiting (76), nausea (48), other skin lesions (90), tingling (52), diarrhea (44), Stevens Johnson syndrome (37), giddiness (32), tremors (27), sedation (25), and muscle dystonias (23).
- A total of 210 reactions have been serious (including 11 deaths), 75 were life threatening, 148 caused or prolonged hospitalization, 7 induced disabilities, and 53 required intervention to prevent permanent impairment/damage.
- Steroid-induced Cushingoid features and posterior capsular cataract, spironolactone-induced gynecomastia and lipodystrophy with hypertriglyceridemia due to antiretroviral drugs were reported. Serious adverse reactions like Steven Johnson syndrome with OTC drugs, phenytion, digitalis induced VPCs, and anaphylactoid reactions due to antivenom venoms were also reported.
- Causality assessment of the reports has been carried out using the WHO UMC criteria as well as the Naranjo's Scale.
Other activities carried out by the Peripheral Center to promote ADR reporting were as follows:

- Meetings were held with clinicians to train and sensitize them to spontaneous reporting.
- The Peripheral Center and its activities were publicized through newsletters of the local Medical Associations.
- The Peripheral Center itself published a newsletter aptly named “Drug Watch” that informed the readers about ADRs, pharmacovigilance, activities of the center, and interesting ADRs reported to it. These were widely distributed to prescribers at the Civil Hospital, Ahmedabad and the private practitioners, other institutions in Gujarat and elsewhere in the country and to the various Centers under NPVP.
- Potential reporters were sensitized about ADR reporting, its importance and other details through posters, personal communication, and letters.
- The website www.pharmacologybjmc.org was launched that informed about the NPVP, the activities of peripheral center, contact details for spontaneous reporting, interesting cases reported every month, and other activities of the peripheral center. The viewers can also report ADE online through this site.
- An International Workshop on Adverse Drug Monitoring was organized in November 2005. Professor Chris Von Boxtel, Emeritus Professor of Clinical Pharmacology at University of Amsterdam, Netherlands inaugurated the workshop. It was well attended by participants from all over the country. It was interactive in nature with group work on ADR reporting and casualty assessment. The sessions were well managed by a experienced faculty. A panel discussion on ADR Reporting in India aptly highlighted the problems of ADR reporting and their possible solutions.

**Pleasures of Running the Center**

The past two years had their own share of pleasures and pains; pleasures that gave us an impetus to move on in spite of all odds and pains. The pleasures have been helping us improve and think beyond the obvious and expected.

Being one of the designated peripheral centers was a joy in itself. Here was an opportunity to pursue an important scientific cause in an organized manner given the backup and finances from the NPVP and of course the official label that went with it. It “authenticated” the whole process and made “believers” from “skeptics” among the prescribers. It was a reinforcement of an existing professional activity that brought recognition to the department and the people involved. The faculty involved focused on this activity with single-minded pursuit; an approach that was lacking until then. Clinical projects and other research were partly directed toward pharmacovigilance. It improved our interaction with like-minded clinicians and other health personnel. The experience gained thus also transformed into a useful academic outcome, when the undergraduate students had their firsthand experience on ADR reporting as a part of their practical curriculum. The postgraduates too got a firsthand experience in interacting with the clinicians and other health personnel. Their experiences and feedback have been a great help for the center in building and revising strategies to make this difficult task doable. They have been trained not only in handling "signals," guiding the reporters, but have also learnt to segregate the reports and build up our own database. Also they are able to analyze the reports for causality; an exercise that can be intriguing and confusing at times.

Running this center may not bring obvious or immediate professional or financial rewards. However, the academic and professional pleasure gained is best experienced than narrated. The spirit of advocacy, education, and interactive learning makes all the trials and tribulations worthwhile. The faculty too gained a lot in terms of expertise in this area. It would not be an overstatement to say that they are now better equipped than before to organize and help build up a Peripheral Pharmacovigilance Center, to handle queries from clinicians, to educate, and share the knowledge gained so far. The next aim of reaching out to other places in Gujarat seems equally uphill, but possible all the same.

**The Pains**

These have been the “lessons” that we learnt and are still learning.

In spite of all these efforts, it would be dishonest on our part to say that all is well. The “spontaneous” part in reporting by the prescribers is somewhat lacking. This is one of the important objectives of the NPVP and hence also of our Center. There could be many reasons for this but primarily it seems to be an apathy and lack of awareness among prescribers. We have observed that the ADRs are reported spontaneously usually after a reminder or following a scientific meeting or other awareness programs. However, they decrease over a period of time. This means that generating spontaneous reports requires a sustained effort. Currently, we have been achieving this goal only partially; a learning for us because it obviously means that more efforts are necessary in this direction. While the initial skepticism and hesitation on the part of reporters is slowly disappearing, recruiting new reporters is still an uphill task. We have observed that a positive feedback from their peers does more to convince the prescribers than our umpteen visits; and we hope to exploit this, if possible.

The services provided to the center by the NPVP, whether financial, academic, or other have been very useful in these two years. But if we are to evolve further, rather than just stagnate at collecting reports and submitting them to higher centers, we could look “upwards” for more. That could be in the form of scientific support, academic resources and training to the people involved. A feedback provided about the status of reports submitted, deficiencies if any and results of casualty assessment provide us an insight about how well or badly we are doing! It can help improve the quality of reports generated at out center and avoid defunct reports. Similarly, a feedback about the activities of the other centers and an interaction with them can widen the scope of the work done and also help sharing of the problems faced and their possible solutions. Additional infrastructure (personnel, a dedicated telephone line and internet connection) can also improve the scope and functioning of the center. Knowing the status of our reports vis-a-vis the global database would be an added feedback that will not only help us introspect and improve, but also provide us a valid authenticated document that could convince the skeptics among the clinicians about the value of their spontaneous
reports. It will certainly make us feel nice if we came to know that we are also a part of the global database.

**Future Plans**

Currently the activities of the center are largely confined to the Civil Hospital Ahmedabad and the city of Ahmedabad. It is necessary to publicize the same throughout Gujarat. We aim to encourage a larger number of prescribers to report spontaneously and to develop a notification culture. We also plan to increase awareness about pharmacovigilance and ADE reporting in health personnel other than prescribers and to encourage reporting from them too. We need to publish the newsletter “Drug Watch” much more frequently. Collating the data collected so far into meaningful statistics is another important task that is keeping us busy at the moment. The expertise gained should also be put to a better use by setting up additional facilities like Drug and Poison Information Services and Drugs and Therapeutics Committee, etc. Lets hope we are able to achieve this and much more!

**References**