Adverse drug reactions at adverse drug reaction monitoring center in Raipur: Analysis of spontaneous reports during 1 year

Preeti Singh, Manju Agrawal, Rajesh Hishikar, Usha Joshi, Basant Maheshwari, Ajay Halwai

Abstract:
BACKGROUND: India is a developing country and adverse drug reactions (ADRs) influence most of the diseases in our population, and monitoring is required due to the paucity of ADRs. The present study was done to analyze the ADRs at the ADR monitoring center (AMC) of tertiary care hospital in Raipur during 1 year.

MATERIALS AND METHODS: Study of ADR monitoring of outpatient and inpatient was a prospective and observational study carried out between September 2015 and August 2016. The ADRs in the form of Individual Case Safety Report (ICSR) was sent to the Indian database (Vigiflow®).

RESULTS: Total ICSRs reported to Vigiflow® were 232 during 1 year. Among them, 63.79% were found to be nonserious and 36.21% were serious. Nearly 45% of ADRs were implicated only due to antimicrobials, which is highest among all other groups of drugs. A maximum number of ADRs were observed in 31–60 years of age group (52.15%). In causality assessment, the probable cases had a higher incidence (67.24%), followed by possible (27.58%) and certain (4.74%). The frequency of ADR reporting at our AMC was low (0.043%) compared to national average. Our AMC shared 0.35% of total ICSRs, which is insignificant ($P < 0.001$) compared to the JSS, Mysore and PGIMER, Chandigarh, AMCs, which have shared most of the ICSRs in Vigiflow®.

CONCLUSIONS: The frequencies of ADRs reporting in our study are less compared to those reported with other similar studies. Underreporting is a very serious concern in Raipur, and Pharmacovigilance Programme of India must intercede to pick up ADRs across the country.

Keywords: Adverse drug reaction monitoring center, adverse drug reactions, individual case safety reports, Pharmacovigilance Programme of India, Vigiflow®

Introduction

All drugs have therapeutic effects and none are absolutely devoid of adverse effects and prescription of them should be judicious and with a satisfactory risk/benefit ratio. Pharmacovigilance has perceived several advancements throughout the world, over the past few decades. The WHO defines “Pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems, including herbal materials.”[1]

Common incidences of adverse drug reaction (ADR) in hospitals are recognized in the patients who are suffering from severe and complex disease process or are on multiple drugs, leading to drug interactions. About 10%–20% ADRs reported are from hospitalized patients which leads to
prolongation of a stay.\cite{4,5} ADR reporting has proven to be a useful tool for patients and health of every population, in reducing morbidity and mortality, but there is more scope for increasing the ADR reporting by the patient or his relative or by non-health-care professional (HCP). Sensitization of Indian urban and rural population is the progressive concern of the Pharmacovigilance Programme of India (PvPI) and is the need of the hour.\cite{3}

In Western countries, a variety of ADR reporting systems are functioning, but in India, it is mostly reported in the form of spontaneous reporting system, without mandatory legal binding. The main aim is to improve and keep vigilance on drugs to enhance patient safety and achieve better health benefits.\cite{6,7}

Indian Pharmacopoeia Commission (IPC) has been functioning as the National Coordination Centre (NCC) for PvPI since April 15, 2011, to monitor the safety of drugs. ADR monitoring centers (AMCs) are functioning in (1) medical colleges and hospitals, (2) medical/central/autonomous institutes, (3) private hospitals, and (4) corporate hospitals. AMCs all over India (total 250; coordinated by NCC-PvPI) are the collecting body of the suspected ADR form, from the HCPs, non-HCPs, or patients directly or through Patient safety Pharmacovigilance Associate (PSPvA). PSPvA follows up the reports to get additional detailed information for scientific assessment.\cite{8} India has a vast ethnic population which suffers from a wide variety of diseases. The complete knowledge and data of ADRs of medicines including herbals, specific to the Indian population lacks, and we have to be dependent on data existing from Western countries. Hence, it is necessary to have a well-organized, voluntary, and broad-based ADR reporting system, to enhance our data and knowledge.\cite{9} At present, PvPI is a very efficient organization for reporting ADRs, but still, underreporting term has not gone from its dictionary. The underreporting of ADR is enormous and a daunting challenge for PvPI.\cite{10,11}

Our AMC is facing the challenge of underreporting of ADRs. It is one of the oldest institutes in this region with various specialities, serving to the health-care needs of a huge population. Our AMC has been functional since the past 2 years, and we have reported only 26 ADRs in the previous year.\cite{12} During the current period of 1 year, we have reported 232 Individual Case Safety Reports (ICSRs), which are approximately ten times of our previous reports. With continuous efforts, we intend to take the number of ADRs to the national level. This study was done to analyze the pattern of ADR reported, and the organs affected as per system organ class (SOC), and the medication suspected to cause them.

Materials and Methods

The study on analysis of ADR reports was a prospective and observational, which was carried out between September 2015 and August 2016. The study was started after the approval from IPC-PvPI, which has provided technical and logistic support for the study and Institutional Ethical Committee of Medical College, Raipur.

The study included all the suspected ADRs which were reported to our AMC, which occurred either with the prescribed drugs or over-the-counter drugs and included both indoor and outdoor patients.

PSPvA visited in OPD and ward of all departments and noted down the ADR in the Suspected ADR Reporting Form (ADR Form) prescribed by NCC-PvPI from the treating physician and nurses. The patients were visited daily until they were discharged from the hospital. If an ADR was noticed by the patients himself/herself, he/she used to fill the patient ADR form and send it to our AMC or reported it by calling at national helpline number 1800180304. We reported all collected ADRs through Vigiflow® software provided by NCC after HCPs confirmation in the form of ICSRs. Some ADRs were also reported from periphery hospitals. If any query or some extra points for ICSRs were required from NCC, the PSPvA contacted the HCP and collected the desired requirements and sent them to NCC. Those ADRs which (1) required hospitalization or prolonged hospitalization, (2) were permanently disabling, (3) leading to congenital anomaly, (4) were life threatening, and (5) led to death, were labeled as serious ADRs. The causality assessment was done using WHO-Uppsala Monitoring Center causality scale by the departmental causality assessment committee.\cite{10} The type, number, seriousness, and pattern of ADR reported, at different levels as per SOC, and the medication suspected to cause ADR has been studied.

The information of the patients and reporters related to ADR was kept confidential.

Statistical analysis

The ADR-related data were calculated as a percentage of the patient population. One-way analysis of variance was used for three or more group comparisons, followed by post hoc Tukey’s test. All statistical calculations were analyzed using statistical software (Sigma Stat, Version 3.5) (DUNDAS SOFTWARE LTD.,© wpcubed, GmbH, Germany and © TE Sub Systems). $P < 0.05$ was considered statistically significant.

Results

During our study period, the number of inpatient and outpatient attendance was 532,514 (data collected from
hospital medical record department), among them 242 ADRs were recognized. However, 232 ICSRs (0.043%) were reported through Vigiflow®. Monthly ADRs were analyzed, number of serious ADRs, and nonserious ADRs defined in Figure 1, which shows December 2015 has the highest number of ADRs, whereas January 2016 has the highest number of serious ADRs.

The demographic tendencies toward ADRs occurrences are 75 (32.33%) males and 157 (67.67%) females, and the causality assessment and ADRs related with different routes are shown in Table 1. The highest percentage of ADRs was reported from gynecology departments (22%). ADRs reported through helpline number were 1.72% of total ICSRs [Figure 2]. The ADRs due to polypharmacy is 66% (more than four drugs per prescription). In our study, only 21.55% ADRs were reported from OPD, whereas 78.45% were from the indoor department, who were admitted mainly for surgery or for multiple diseases simultaneously requiring prolonged stay.

Numbers of ADRs by various pharmacological classes of drugs are summarized in Figure 3. Among them, only antimicrobials have acquired approximately half of the ADRs (45% ADRs). The types of ADRs in various organ systems (SOC) have been summarized in Table 2. ADRs of skin and subcutaneous tissue disorders were greatest among all SOCs.

In the period of 1 year, total ICSRs submitted by some leading medical colleges in India by various state AMCs and our AMC with including pharmaceutical companies were 66,056. The monthly ICSRs have been compared [Figure 4]. AMCs of JSS, Mysore and PGIMER, Chandigarh have contributed 3.68% and 3.66% ICSRs, respectively, in Indian database (Vigiflow®), whereas our AMC shared a small proportion of 0.35% of ICSRs in Indian database. There is statistically significant difference ($P ≤ 0.001$) between JSS, Mysore and PJNM, Raipur, reporting of ADRs through Vigiflow.

**Discussion**

Joint efforts by over 100 member countries in the Pharmacovigilance Programme have helped the WHO international database of suspected ADRs, VigiBase®, which has reached 14 million ICSRs.[11] In Indian database, Vigiflow®, a total number of 66,056 ICSRs were reported from various AMCs and pharmaceutical companies since September 2015 to August 2016, according to Monthly Progress Report (PvPI, IPC).[12] In this regard, our AMC contributed 232 (0.352%) of whole ICSRs in Vigiflow® during 1 year. This reporting ADRs data are insignificant compared to JSS, Mysore and PGIMER,

### Table 1: Demographic, route of administration, and causality of adverse drug reactions

| Demographic parameter | Number of ADRs (%) |
|-----------------------|-------------------|
| **Age wise**          |                   |
| 1-18                  | 25 (10.78)        |
| 19-30 years           | 71 (30.6)         |
| 31-60 years           | 121 (52.16)       |
| >60 years             | 15 (6.47)         |
| **Sex wise**          |                   |
| Male                  | 75 (32.33)        |
| Female                | 157 (67.67)       |
| **Route of drug administration wise** | |
| Oral                  | 97 (41.81)        |
| Parenteral            | 132 (56.89)       |
| Topical (local)       | 3 (1.29)          |
| **Causality assessment** |               |
| Certain               | 11 (4.74)         |
| Probable              | 156 (67.24)       |
| Possible              | 64 (27.58)        |
| Likely                | 1 (0.43)          |

ADRs=Adverse drug reactions
Chandigarh AMC, who have contributed a maximum number of ICSRs in Vigiflow® which is 3.63% and 3.33%, respectively. The AMCs of other states such as Madhya Pradesh (GMC, Bhopal and SAIMS, Ujjain), Ranchi, CG, and Guwahati has contributed only 0.14% and 0.89%, 0.23%, 0.35%, and 0.39% respectively [Figure 4]. Underreporting of ADRs from these states may be due to poor literacy rates, underdeveloped health-care facilities, and high poverty. Moreover, the AMCs of these states are in their infant stage. Continuous awareness programs for HCPs and public will improve and increase the number of ADRs reporting. Although HCPs have good knowledge and awareness on adverse reaction reporting and pharmacovigilance, their practices need to be improved.

The incidence rate of ADRs in our hospital was 0.044%. The total number of patients registered in our OPD and IPD during this period was 531,877 (data collected from hospital medical record department). The occurrence rate of ADR in various studies across the globe is in

**Table 2: Frequency and types of adverse drug reactions reported by adverse drug reaction monitoring center according to system organ class**

| SOC | Number of ADRs | Different types of ADRs |
|-----|----------------|------------------------|
| Cardiac disorders | 8 | Tachycardia, palpitation, bradycardia |
| Ear and labyrinth disorders | 2 | Vertigo |
| Eye disorders | 2 | Oculogyric crisis, peri-orbitaledema |
| Gastrointestinal disorder | 17 | Diarrhoea, vomiting, flatulence, lip swelling, hypersalivation, difficulty in swallowing of liquid, pharyngitis |
| General disorders and administration site conditions | 35 | Rigors, shivering, flushing, edema face, swelling in body, malaise, fatigue, chest pain, hyperacidity, fluid retention |
| Hepatobiliary disorders | 1 | Hepatitis |
| Immune system disorders | 5 | hypersensitivity reactions, anaphylactic reaction |
| Injury, poisoning, and procedural complications | 2 | Organophosphorus poisoning, death |
| Metabolism and nutrition disorders | 2 | Loss of appetite |
| Nervous system disorders | 10 | Dizziness, giddiness, numbness in fingers and legs, headache, faint |
| Pregnancy, puerperium, and perinatal conditions | 1 | Accident by bike due to impairment in hands |
| Renal and urinary disorders | 1 | Haematuria |
| Reproductive system and breast disorders | 1 | Menorrhagia |
| Respiratory, thoracic, and mediastinal disorders | 36 | Respiratory distress, dyspnoea, breathing difficulty, aspiration, asthma, pneumonia, burning sensation of throat, bronchospasm, hypoxia |
| Skin and subcutaneous tissue disorders | 95 | Itching and urticaria, eczematous lesions, erythematous rash, alopecia, maculopapular rashes, erythematous rashes, bullous drug eruptions, desquamous scaly lesions on the whole body, purpura, SLE, StevenJohnson's syndrome, hyperpigmentation, lepra reaction, fixed drug eruption |
| Vascular disorders | 12 | Thrombophlebitis, hypertension, hypotension |
| Product issues | 2 | Inefficacy |

SOC=System organ class, SLE=Systemic lupus erythematosus, ADRs=Adverse drug reactions
Polypharmacy is very prevalent worldwide, so in India and also in our AMC. It was observed that prescribing single or two drugs causes very low or no ADRs. On the other hand, as the number of prescribed drugs increases, the ADRs also increase. In our study, 155 prescriptions (66%) contained four or more drugs, which supported that polypharmacy increases the incidence of ADRs. Antimicrobials have the lion's share among the drugs causing ADR, and our study also revealed an incidence of 45% ADRs due to antimicrobials. Similarly, prolonged hospitalization due to comorbidity added to the burden of ADRs.

The reporting frequency of ADRs by nursing staff was low (21.98%) compared with doctors (82.32%) and the patient's contribution was very low (4.31%) even after sensitization to all of them. This observation was also supported by a study conducted in Karnataka state. This may be due to the high workload or inattention toward ADRs reporting or less confidence and fear for legal implications in spite of the fact that there are no legal implications for ADR reporting. In addition, there is a well-maintained confidentiality about the reporter and patients.

As per SOC in our study, ADRs of skin and subcutaneous tissue disorders, respiratory, thoracic, and mediastinal disorders were 95 (41%) and 36 (15.5%), respectively. This finding is similar to other studies where skin and subcutaneous tissue disorders ranked highest. Among all the ADRs, none was newly detected reaction to the associated drug and all were well known and documented. We also reported some specific ADRs such as systemic lupus syndrome and Stevens–Johnson syndrome due to isoniazid and ceftriaxone, respectively.

PvPI must focus on multiple approaches for sensitizing everyone who is either consuming or dispensing or prescribing medicines. All should be made aware of their role in ADRs reporting and its importance in the future for their health benefit. Sensitization process is not a 1-day process. It should be continuous and should focus on some basic points such as (1) legal aspects: as HCPs have a fear of litigation. They feel that the occurrence of ADR is due to wrong drug prescribed or due to drug interaction in their prescription; (2) complacency: HCPs believe that before a medicine is introduced in the market, its ADRs are already mentioned, so similar ADR of a drug needs not be reported again; (3) hesitancy: believing that if there is certainty of the ADRs to occur by the use of a particular drug, then reporting should be done; (4) unimportance: assuming that a single ADR report will make no change; (5) unawareness: they think that reporting should be done of just serious or new ADRs; (6) excuses: like lack of time, why should I report, whom to report, and type of attitude should be changed; or (7) disinterestedness. Some approaches such as small financial incentives (rewards for reporting) to doctors and nurses may support ADRs reporting enthusiasm. Felicitation of HCPs who have reported maximum ADRs during get together programs of the hospitals will motivate other staff. Approaches such as the ADRs monitoring network within hospitals, educational programs for physicians and medical students, making ADRs reporting compulsory for nurses and paramedical staff, workshop and telephonic conversation, and use of the mobile app (for ADR reporting) may help in improving ADRs reporting. Doctors (interns and house officers), nurses, pharmacist, and residents also need to be more actively involved in reporting ADRs, to increase the reporter base. An intensive monitoring approach by PSPvA with the help of HCPs can improve the detection of ADRs and help in reinforcing the ICSRs in Vigiflow. Teaching of pharmacovigilance to undergraduate and postgraduate students in pharmacology and hands-on training on how to fill up the form, perform causality assessment, and knowledge about Vigiflow® will improve ADRs reporting. Pharmacovigilance is a lifetime process and should not stop, once an ADR is reported or well known among populations or at any stage of a life cycle of drug and human beings. Pharmacovigilance plays a vital role in our health’s safety and should be the moral responsibility of society as a whole to report ADRs.

Conclusions

Our study finds that the incidence of ADR reporting in our AMC is insignificant, compared to that reported by other AMCs. The incidence of ADR reported by various studies across the world is 6%–20%, whereas in India, it is up to 3%. HCPs have good knowledge and awareness on ADR, but their practice in the form of reporting needs to be improved. Underreporting is a very serious concern in our AMC, and PvPI must initiate newer methodologies to enhance reporting of ADRs in our country.

Acknowledgment

The authors are indebted to The IPC, NCC-PvPI, Dr. BRAM Hospital and Department of Pharmacology.
Financial support and sponsorship
This study was financially supported by IPC, PvPI, and Dr. BRAM Medical College, Raipur, Chhattisgarh, India.

Conflicts of interest
There are no conflicts of interest.

References
1. Vivekanandan K, Thota P, Janarthanan VV, Singh GN. Pharmacovigilante’s in the pharmacovigilance programme of India: Ideal qualities and skills. J Young Pharm 2016;8:291-2.
2. Gor AP, Desai SV. Adverse drug reactions (ADR) in the inPatients of medicine department of a rural tertiary care teaching hospital and influence of pharmacovigilance in reporting ADR. Indian J Pharmacol 2008;40:37-40.
3. van Hunsel F, Härmäark L, Pal S, Olsson S, van Grootheest K. Experiences with adverse drug reaction reporting by patients: An 11-country survey. Drug Saf 2012;35:45-60.
4. Datta S, Sengupta S. An evaluation of knowledge, attitude, and practice of adverse drug reaction reporting in a tertiary care teaching hospital of Sikkm. Perspect Clin Res 2015;6:200-6.
5. Mittal N, Mittal R, Gupta MC. An overview of the pharmacovigilance system in India. Clin Res Regul Aff 2016;33:4-8.
6. Kalaiselvan V, Kumar R, Singh GN. Indian pharmacopaedia commission’s partners for promoting public health. Adv Pharmacoepidemiol Drug Saf 2015;4:181.
7. Tandon VR, Mahajan V, Khajuria V, Gillani Z. Under-reporting of adverse drug reactions: A challenge for pharmacovigilance in India. Indian J Pharmacol 2015;47:65-71.
8. Gahr M, Eller J, Connenmann BJ, Schönfeldt-Lecuona C. Subjective reasons for non-reporting of adverse drug reactions in a sample of physicians in outpatient care. Pharmacopsychiatry 2016;49:57-61.
9. Agrawal M, Hishikar R, Joshi U, Halwai A, Toddar TL, Khubchandani V, et al. Adverse drug reaction scenario at ADR monitoring centre of tertiary teaching hospital at Raipur. Indian J Pharmacol 2015;2:169-75.
10. Kumar BN, Nayak K, Singh H, Dulhani N, Singh P, Tewari P. A pharmacovigilance study in medicine department of tertiary care hospital in Chhattisgarh (Jagdalpur), India. J Young Pharm 2010;2:95-100.
11. Upsala Monitoring Centre 14 Million ICSRs in Vigibase. Available from: http://www.whoicumc.org/DynPage.aspx?id=105196& mni=7347&mnm=7499&mnm3=7248&news id=16863. [Last accessed on 2016 Sep 30].
12. Indian Pharmacopoeia Commission. PvPI Updates. Monthly Progress Report. Available from: http://www.ipc.nic.in/index2.asp?sid=556&sublinkid=459&lang=1&EncHid=. [Last accessed on 2016 Nov 01].
13. Sönничsen A, Trampisch IS, Rieckert A, Piccoliori G, Vögele A, Flamm M, et al. Polypharmacy in chronic diseases-reduction of inappropriate medication and adverse drug events in older populations by electronic decision support (PRIMA-eDS): Study protocol for a randomized controlled trial. Trials 2016;17:57.
14. Ahmed B, Nanji K, Mujeeb R, Patel MJ. Effects of polypharmacy on adverse drug reactions among geriatric outpatients at a tertiary care hospital in Karachi: A prospective cohort study. PLoS One 2014;9:e112133.
15. Thomas BM, Tamang JK, Tom C, Nanjwade BK. A prospective study on extent of polypharmacy leading to adverse drug reactions in geriatrics in a tertiary care hospital. World J Pharm Sci 2016;5:1555-7.
16. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard medical practice study II. N Engl J Med 1991;324:377-84.
17. Salvo F, Miroddi M, Alibrandi A, Calapai F, Cafo V, Mancari F, et al. Attitudes and opinion about adverse drug events of women living in a city of South Italy. Pharmacology 2013;91:173-7.
18. Sahu RK, Yadav R, Prasad P, Roy A, Chandrakar S. Adverse drug reactions monitoring: Prospects and impending challenges for pharmacovigilance. Springerplus 2014;3:695.
19. Nair NP, Chalmers L, Peterson GM, Bereznicki BJ, Castelino RL, Bereznicki LR. Hospitalization in older patients due to adverse drug reactions—the need for a prediction tool. Clin Interv Aging 2016;11:497-505.
20. Rajesh R, Vidyasagar S, Varma DM. An educational intervention to assess knowledge attitude practice of pharmacovigilance among health care professionals in an Indian tertiary care teaching hospital. Int J PharmaTech Res 2011;3:678-92.
21. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. Br J Clin Pharmacol 2008;65:210-6.
22. Desai CK, Iyer G, Panchal J, Shah S, Dikshit RK. An evaluation of knowledge, attitude, and practice of adverse drug reaction reporting among prescribers at a tertiary care hospital. Perspect Clin Res 2011;2:129-36.
23. Goldstein LH, Berlin M, Saliba W, Elias M, Berkovitch M. Founding an adverse drug reaction (ADR) network: A method for improving doctors spontaneous ADR reporting in a general hospital. J Clin Pharmacol 2013;53:1220-5.
24. Nikfarjam A, Sarker A, O Connor K, Ginn R, Gonzalez G. Pharmacovigilance from social media: Mining adverse drug reaction mentions using sequence labeling with word embedding cluster features. J Am Med Assoc 2015;313:2671-81.
25. Yang CC, Yang H, Jiang L, Zhang M. Social media mining for drug safety signal detection. Proceedings of the 2012 International Workshop on Smart Health and Wellbeing. New York, USA: ACM; 2012. p. 33-40.
26. Lopez-Gonzalez E, Herdeiro MT, Piñeiro-Lamas M, Figueiras A; GREPHEPI group. Effect of an educational intervention to improve adverse drug reaction reporting in physicians: A cluster randomized controlled trial. Drug Saf 2015;38:189-96.
27. Arici MA, Gelal A, Demiral Y, Tuncok Y. Short and long-term impact of pharmacovigilance training on the pharmacovigilance knowledge of medical students. Indian J Pharmacol 2015;47:436-9.
28. Griffith R. Nurses must report adverse drug reactions. Br J Nurs 2013;22:484-5.
29. Herdeiro MT, Ribeiro-Vaz I, Ferreira M, Polónia J, Falcão A, Figueiras A, et al. Workshop-and telephone-based interventions to improve adverse drug reaction reporting: A cluster-randomized trial in Portugal. Drug Saf 2012;35:685-695.
30. Kuchya S, Kalaiselvan V, Kaur J, Singh GN. Mobile application an approach to enhance easy adverse drug reactions reporting in India. Health Technol 2016;6:157-8.