Drug safety alerts of pharmacovigilance programme of India: A scope for targeted spontaneous reporting in India

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Abstract

Background: The National Coordination Centre-Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopoeia Commission works under the aegis of Ministry of Health and Family Welfare, Government of India. It promotes patient safety in India and also supports postmarketing surveillance programs. Currently, almost hundred thousand case reports are submitted to NCC-PvPI each year through its 250 ADR Monitoring Centers (AMCs) located across India, and India is the one of the top ten contributor countries under WHO-Uppsala Monitoring Centre since 2012 and start issuing drug safety alerts from March 2016.

Aim: This study aims to highlight the drug safety alerts issued by NCC-PvPI from March 2016 to June 2017 and urgent need for further monitoring by adopting targeted spontaneous reporting (TSR) methodology at AMCs and its impact on the NCC's drug safety database, i.e., VigiFlow in India.

Methodology: A retrospective analysis was done for the reported unlisted ADRs by various AMCs to PvPI through VigiFlow, i.e., individual case safety report (ICSR) management system at NCC, where these unlisted drug-ADR combinations considered and issued as drug safety alerts for further reporting these to NCC, if any detected at healthcare settings during routine clinical practice by healthcare professionals.

Results: From July 2011 to June 2017, NCC-PvPI was collated 250,787 ICSRs and contributed to WHO international drug safety database, i.e., VigiBase, from these ICSRs; NCC-PvPI was issued 56 drug safety alerts from March 2016 to June 2017.

Conclusion: In India, spontaneous reporting of ADRs existed since 1998 under passive surveillance method, but there is an urgent need to initiate TSR, which is a complementary method to spontaneous reporting on these drug safety alerts for further regulatory action by Central Drugs Standard Control Organization.

Keywords: Drug safety alerts, pharmacovigilance, Pharmacovigilance Programme of India, spontaneous reporting, targeted reporting

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INTRODUCTION

India is the member country in the WHO Programme for International Drug Monitoring (WHO-PIDM), i.e., WHO-Uppsala Monitoring Centre, Sweden since 1998.[1] Ministry of Health and Family Welfare, Government of India has started a nationwide Pharmacovigilance Programme of India (PvPI) in the year 2010 in All India

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Institute of Medical Sciences as National Coordination Centre (NCC) with 22 regional adverse drug reaction monitoring centres (AMCs) across the country. Indian Pharmacopoeia Commission, an autonomous body under the Ministry of Health and Family Welfare, located at Ghaziabad functioning as NCC for PvPI since 2011 further NCC, which was extended to a total number of 250 AMCs by the year 2017.[2] At present, India is the only country having maximum number of regional AMCs and also one of the largest contributors of adverse drug reactions (ADRs) among the top ten countries under WHO PIDM. All these AMCs were well connected with WHO PIDM's global individual case safety report (ICSR) database, i.e., VigiBase[3] through their individual ICSR management system, i.e., VigiFlow.[4]

During the last six years, PvPI contributed 250,787 ICSRs out of the VigiBase of the total 8,535,518 globally. From the contributed data, PvPI identified 56 drug safety alerts[5] based on the voluntary reporting of ADRs by various healthcare professionals and consumers to PvPI through its AMCs, on PvPI-Helpline number – 1800-180-3024 and Android Mobile application for reporting of ADRs; these methods come under spontaneous ADR reporting system. Hence, there is wider scope for practising physicians, clinical pharmacists, nurses, and also marketing authorization holders of their products which are available in their drug safety databases for reporting to any of the AMCs or NCC-PvPI for promoting patient safety in the country with the help of these drug alerts.

The World Health Organization (WHO) adopted "Targeted Spontaneous Reporting (TSR)" as a complementary methodology to spontaneous reporting system in 2010, but it can be applied in a defined setting. TSR, also known as stimulated reporting, is different from spontaneous reporting that focuses on collecting ADRs in a well-defined group of patients taking specific drugs. TSR method provides a comprehensive monitoring method, which is affordable and practicable in healthcare settings with limited human and financial resources (WHO 2012).

At present, ADR-reporting mode adopted by PvPI is "Spontaneous Reporting" which is confined mainly to reporting of suspected adverse reaction to a particular drug. Spontaneous reporting has many limitations as this mode of reporting captures only a small fraction of the adverse events. TSR thus helps to overcome the main disadvantages of spontaneous reporting, that is underreporting and the inability to calculate rates, while maintaining simplicity of use, low cost and linkage to existing systems. TSR represents an additional strength to the routine monitoring of outcomes of patients and can provide some measure of rates and incidences and also acts as bridge between public health programs to PV centers. Keith *et al*. (2014) in their study started and developed TSR as stimulated reporting for studying impact of US Food and Drug Administration (FDA) alerts on adverse event reporting. In this study, 100 drugs were chosen, which were released between 2001 and 2010.[6] Similar study is planned to be carried out at PvPI to find the impact of this drug alerts with emphasizing the need of TSR.

METHODOLOGY

At NCC, all these ICSRs shall be processed as per the standard operating procedures of PvPI, and then, the drug safety data shall be contributed to VigiBase for further identification of drug safety signals at global level. The collected ADR reports by AMCs are communicated to NCC-PvPI through the provided VigiFlow tool of AMCs. Secondary processing of ICSRs at NCC-PvPI involves triage checking, checking for essential required items, to upgrade documentation grading completeness score of ICSRs as per the WHO-UMC VigiGrade algorithm.

The reported ICSRs of all AMCs to NCC-PvPI filter unlisted ICSRs (one ICSR shall contain multiple drug-ADR combinations such as one drug-one ADR, one drug-multiple ADRs, multiple drugs-one ADR, multiple drugs-multiple ADRs reported in one patient as ICSRs) through the VigiFlow, then these unlisted ICSRs segregated as unlisted drug-ADR combinations for further validating it as unlisted drug-ADR combination/drug alerts. NCC-PvPI shall review the various drug information resources which includes primary, secondary and tertiary along with information from the marketing authorization holder's product information leaflets and authorized government websites. PvPI also compares the data of drug-ADR combinations with VigiLyze database and publications from other countries National Centres for pharmacovigilance.

Information component value (IC) gives a further information for processing the obtained drug alerts to the decision-making in signal, and other quantitative methods for the identification of signals for ICSRs also existed in India. The IC is a Bayesian measure to assess the strength of the quantitative dependency between a specific drug and a specific ADR. As with any Bayesian inference, inference of the IC is drawn considering its posterior distribution. The IC_{025} is the lower limit of the 95% highest posterior density interval of the IC. It was assumed that the drug and ADR were independent. This method requires no assumption for the number of cases for a particular drug-ADR

combination. The extra variability in the estimation of the strength of the association was controlled in the case of small number of drug-ADR combinations. The PvPI has the privilege to access VigiMine, a WHO-UMC tool, to calculate ICs for Indian ICSRs.[7,8]

These drug alerts are circulated to all stakeholders/partners of the NCC-PvPI, and the AMCs follow all the patients receiving the drugs-ADR combination given as alerts at their respective sites. Any ADR among the drug alerts of PvPI are notified, especially on the follow-up. This focus on particular group stems the initiation of the TSR among the AMCs in implementing the country wide monitoring as well as sensitizing the HCPs for pharmacovigilance.

RESULTS

A total of 56 India-specific drug alerts were identified by PvPI till June 2017 and the IC values are identified for the same. The various drug alerts identified by PvPI and IC values of these drug-ADR combinations are shown in Table 1.

Table 1 shows strong statistical connection between drug and ADR combinations with their respevtive IC values. All the drug alerts were monitored closely for TSR, and in few drug-ADR combinations, the increase in the number of reports was observed. The increase in the number of reports shows and gives spotlight on identification of signal also which is main advantage of the TSR. Furthermore, the increase in number of reports shows the awareness of PvPI program in identification of the rare ADRs.

NCC-PvPI implemented the quantitative methods for the identification of signals for ICSRs in India, and information component value is important determinant among the criteria. In the year 2016 PvPI planned the TSR method to be adopted initially among patients seeking care from one of its regional pharmacovigilance center, i.e., postgraduate institute of medical education and research and their catchment healthcare facilities. The purpose of this study was to pilot TSR using the drug alerts of drugs listed above and to enhance pharmacovigilance within the AMCs and nearby centers associated with AMCs. For the pilot study, patients receiving drugs among the list will be targeted and monitored.

DISCUSSION

The pilot study conducted observed to be beneficial, and the acceptance of the HCPs in reporting ADRs shows the pattern of increase in trend. This study will also be expanded to other AMCs for conducting the same observations among HCPs and to establish pharmacovigilance system. To enhance the TSR, the health professionals managing patients were trained on the TSR methodology and other monitoring as well as any safety concerns. To supplement the training, support supervision will be conducted regularly and involved personnel from both the PvPI and AMC. During support supervision, review meetings with the pharmacovigilance center focal persons will be held, and strategies for strengthening pharmacovigilance in the hospitals can be reviewed.

TSR is considered likely to build on the gains that had already proved patient safety in public health programs in promoting the role of pharmacovigilance as the best healthcare practice. Monitoring patients on various drugs for a possible increased risk of safety alerts by using this TSR method is crucial.[9] TSR promotes to build a definite set of attributes and provides economical, feasible comprehensive monitoring method and sustainable in settings with limited financial and human resources. It also encourages evidence-based decision-making in PV as a best practice that safeguards public healthcare system.

TSR may be modified either to report all suspected reactions in the defined population or to focus only on specific reactions of particular concern. This serves to limit the reporting workload to those adverse events that are most significant to individuals and to the programs. Poor adherence to treatment due to adverse events such as nausea can be included as one of the targeted events in the TSR concept for priority reporting. It is mostly useful in the targeted follow-up of patients with rarely identified ADRs which shall be further investigated from patients in tertiary care teaching hospitals, compared with routine spontaneous reporting.

TSR increase reporting rates by targeting, training, and mentioning reporters at selected high caseload clinics and by task shifting the reporting to nonphysician cadres of healthcare workers such as nurses, pharmacists, pharmacy technicians, and patients living with various comorbid conditions.[10] To address underreporting of ADRs due to drugs, the PvPI, in support with the AMCs planned to perform the TSR approach in the year 2016 as a complementary method to the traditional spontaneous reporting method. TSR is a variant of spontaneous reporting that focuses on capturing ADRs in a well-defined group of patients on treatment.[10]

CONCLUSION

As the initiative was taken by PvPI in identifying the drug alerts which gives a ray of hope in directing the research

Table 1: Details of drug – ADR combinations

Suspected drugs	Adverse reactions	Drug-ADR combinations	IC value	IC_{025} value
Phenytoin	Angioedema	9	−1.05	−2.14
Phenytoin	Osteoporosis	3	0.19	−1.86
Nicorandil	Risk of ulcer complication	1	0.83	−2.96
Olanzapine	Hyponatremia	3	−2.12	−4.18
Crizotinib	Risk of cardiac failure	2	2.21	−0.38
Roflumilast	Gynecomastia	1	1.58	−2.21
Clozapine	Neutropenia	3	−0.01	−2.06
Disulfiram	Erythroderma	2	2.26	−0.32
Peginterferon-alpha-2a	Vasculitis	1	1.56	−2.24
Piperacillin and tazobactam	Vision abnormal	2	−1.18	−3.77
Mometasone furoate, topical	Hypertrichosis/hirsutism, skin depigmentation	2	2.19	−0.4
		1	1.42	−2.38
		4	3.01	1.27
Ranibizumab	Myocardial infarction	2	1.98	−0.6
Amphotericin B	Bone marrow depression	3	1.52	−1.07
Doxorubicin	Photosensitivity reaction	2	−1.33	−3.92
Crizotinib	Pneumonitis, hepatic encephalopathy	1	1.58	−2.23
		1	1.57	−2.23
Febuxostat	Allergic vasculitis	1	1.58	−2.22
Oxcarbamazepine	SIADH	1	1.54	−2.25
Artemether and lumefantrine	Stevens–Johnson syndrome/toxic epidermal	2	1.63	−0.95
	necrolysis	1	1.31	−2.48
Cefixime	AGEP	3	2.32	0.27
Hepatitis B immune globulin (human)	Encephalopathy	1	1.58	−2.22
Cefotaxime	Anaphylactic shock	9	2.51	1.41
Lacosamide	Red man syndrome	1	1.51	−2.29
Dimethyl fumarate (fumaric acid)	Osteonecrosis	1	1.58	−2.22
Sodium citrate/diphenhydramine hydrochloride/ammonium chloride	Myocardial infraction	3	2.71	0.66
Cabergoline	Steven–Johnson syndrome	1	1.37	−2.42
Amlodipine	Alopecia	2	−4.37	−6.95
Nitrofurantoin	DRESS syndrome	1	1.23	−2.56
Cefoperazone sulbactam	AGEP	1	1.19	−2.61
Cefixime	Anal ulcer	1	0.46	−3.34
Atenolol	Dermatitis lichenoid	3	2.51	0.46
Olanzapine	DRESS syndrome	3	−1.38	−5.17
Meropenem	Hypokalemia	5	1.84	−0.69
Montelukast	Tinnitus	1	1.19	−2.61
Cefepime	Dermatitis lichenoid	1	1.5	−2.3
Losartan	Burning micturation	2	1.99	−0.6
Amisulpride	Tinnitus	1	0.78	−3.01
Carbamazepine	Bruxism	3	2.4	−0.35
Clomipramine	Melasma	1	1.35	−2.45
Glimepiride	Lichenoid drug eruption	1	1.15	−2.65
Metoprolol	Lichenoid drug eruption	1	1.21	−2.59
Levamisole	Skin exfoliation	1	1.57	−2.27
Deferasirox	Osteoporosis	1	1.45	−2.35
Ambroxol	Lacrimation	1	1.58	−2.22
Lurasidone	Thrombocytopenia	1	1.5	−2.3
Etoricoxib	Skin hyperpigmentation	1	−0.46	−4.26
Dexamethasone	Hiccups	8	2.55	1.39
Cabergoline	Skin hyperpigmentation	1	1.37	−2.43
Sodium valproate	Psoriasis	2	−0.01	−2.60
Amoxycillin	Eye irritation	2	0.53	−2.05
Tinidazole	Hyperpigmentation	9	2.09	0.99
Amlodipine	Psoriasis	7	2.56	1.3
Hydroxyzine	Bullous pemphigoid	1	1.57	−2.23
Amitriptyline	Gingival discoloration	1	1.55	−2.25
Paracetamol	Baboon syndrome	1	1.04	−0.33
Lamivudine	Hearing loss (hypoacusis)	3	−0.53	−2.58
Mebeverine	Retrosternal pain	1	1.58	−2.21

DRESS=Drug reaction with eosinophilia and systemic symptoms, AGEP=Acute generalized exanthematous pustulosis, ADR=Adverse drug reaction, SIADH=Syndrome of inappropriate antidiuretic hormone secretion

in pharmacovigilance toward the TSR, it may also ensure involving multiprofessional collaborations and more patient care faculty involvement in complete healthcare provision to the general public. Hence, the same culture needs to be

adopted in India which helps in attaining a better patient safety with more focused surveillance by considering these drug alerts as trigger resources or evidence-based ADR reporting as drug safety signals by national drug regulatory authority, i.e., Central Drugs Standard Control Organization in India.

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Conflicts of interest

There are no conflicts of interest.

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