ORIGINAL ARTICLE

Critical Analysis of Quality Adverse Drug Reaction Related Published Reports in Indian Biomedical Journal

Iram Kahkashan, Shabnam Chowdhary, Vishal R. Tandon, Sharminder Kaur, Vijay Khajuria, Z. Gillani

Abstract

To critically analyze the quality of medical contents of published ADR reports in Indian biomedical Journals. The current descriptive observational study evaluated case reports of last 2 years published in two standard Indian journals from the field of pharmacology and Pharmacotherapeutics with PV as scope. The international society of epidemiology (ISPE) and the international society of pharmacovigilance (ISoP) joint recommendations for submitting ADR's for publication were used. Out of 96 ADE's 86.45% were ADRs, 10.41% drug interactions & 3.13% medication errors. 22.91% were new drugs and 78.12% were due to old drugs. 66.67% & 25.00% of ADRs were rare and unusual respectively. 14.58% of the cases was seriousness/life threatening and 4.17% of cases were fatal. 14.5% & 19.7% cases were type A & B reactions respectively. 98.95% of the reports provided information about drug dosage, duration, route and formulation. Naranjo and WHO scale were not used in 21.88% and 56.25% of cases respectively. Severity scale and preventability scale were not applied in 90.63% and 94.79% of cases. Temporal relationship was not clear in 4.21% cases while medical contents were inadequate in 42.71% of cases. In 83.33% dose response relationship was not seen. Pictorial evidence was lacking in 48.9% & drug estimation in 92.71% cases. Other offending drug or pathology was present in 53.13% cases. In 19.79% of cases investigations were present but inadequate.The quality & Medical contents of published ADR reports in Indian journals are inadequate in various aspects which need improvisation.

Key Words

Quality , ADR, Biomedical Journal, Case Report

Introduction

The Adverse Drug Reaction (ADR) related case reports are commonly published in biomedical literature. They can prove very helpful to pharmacovigilance program of India (PvPI) and prescribers to enhance drug safety in clinical practice. Their utility to PvPI is because most of these reports pertain to recently introduced drugs, rare, unusual, severe/serious, fatal ADRs and adverse events due to medication errors, & drug interactions. Thus, a database of such ADRs may help PvPI to identify signals early in comparison to conventional approach of spontaneous reporting system. These reports often do not follow guidelines and poor quality of these reports fail significantly to serve their purpose, in spite of availability of Joint recommendations /guidelines of the international society of epidemiology (ISPE) and the international society of pharmacovigilance (ISoP) as well as CARE guidelines for submitting adverse event reports for publication. (1, 2) There are some studies which point out that published ADR case reports especially from non specialized journals lack important medical information. (3, 4) The problem actually starts at the outset the way inadequate medical contents are filled up by the health workers while reporting spontaneous case reports. (4) To address the said problem WHO has started a feedback system to members countries about their average medical content/completeness score of individual case safety reports (ICRS). (5) Thus and attempt to Critical analyse the published ADR case reports shall go a long way in providing feedback to leading medical journals to introspect and improvise in publishing the ADR's as per the recommended guidelines and shall also prove useful for PvPI.

Material & Method

The current descriptive observational study was conducted after IEC permission vide no. ---- by evaluating case reports of last 2 years published in two standard

From the Department of Pharmacology, Govt. Medical College Jammu, J&K India 180001

Correspondence to : Dr Vishal Tandon Associate Professor , Department of Pharmacology Govt Medical College, Jammu J&K India

most leading Indian, open access, peer reviewed journals indexed in Medline from the field of pharmacology and Pharmacotherapeutics with PV as scope. 96 obtained adverse drug events (ADE's) were evaluated by taking their print outs and reading them thoroughly. The data was categorised for subgroup analysis as per standard operating procedure (SOP) of PvPI. The international society of epidemiology (ISPE) and the international society of pharmacovigilance (ISoP) joint recommendations/guidelines for submitting ADR's for publication were used to critically analyze the quality of medical contents of published ADR reports. (1)

Statistical Analysis

Descriptive statistical analysis was carried out with the help of computer software SPSS Version 15 for windows.The data was expressed in n (%).Chi square test was applied for some of the parameters to prove their statistical significance. P value < 0.05 was considered significant.

Results

Out of 96 ADE's 86.45% were due to drugs themselves, 10.41% drug interactions and 3.13% medication errors. ADE's due to recently introduced drugs were seen in 22.91% cases and 78.12% were due to old drugs. 66.67% & 25.00% were rare and unusual respectively. 14.58% of the cases was seriousness/life threatening and 4.17% of cases were fatal. 14.5% & 19.7% cases were type A & B reactions respectively, whereas, a major chunk compromising of 63.5% could not be classified. 78.95% of cases recovered as was depicted in outcome of published reactions. According to Naranjo scale 66.66% of cases fell in probable while as only 7.29% and 4.17% cases were definite and possible respectively. Similarly according to the WHO/UMC scale 35.42% cases were probable and 5.21% & 3.13% were certain and possible respectively. **(*Table-1*)**

While critically analysing the data the rationality of publishing ADE was usual in 8.33% of cases. 98.95% of the reports provided information about drug dosage, duration, route and formulation with 100% using non proprietary names. Naranjo and WHO scale were not used in 21.88% and 56.25% of cases respectively. Severity scale and preventability scale were not applied in 90.63% and 94.79% of cases. Temporal relationship was not clear in 4.21% cases while as medical contents of the report were inadequate in 42.71% of cases. Detail about management was not clearly mentioned in 10.42% and possible hypothesis was not clear in 6.25% cases.

In 83.33% of the published case reports dose response relationship was not seen. The data was not reported according to the PvPI - SOP in 92.71% of cases. Pictorial evidence was not documented in 48.9% of the cases whereas; only 6.25% cases did not require them.

Drug level estimation was not done in 92.71% cases and majority failed to document the availability of the facilities. Other offending drug or pathology which could have contributed to the ADE was present in 53.13% cases. De-challenge was done in 90.62% while as re-challenge was done only in 12.5% of cases. Re-challenge was not mentioned in 65.6% of cases. While in 7.2% and 10.4% of cases it was not done due to ethical reasons and re-challenge not done but mentioned respectively. 3.13% of the cases lacked relevant investigations whiles as in 19.79% of cases investigations were present but inadequate. **(*Table-2*)**

The detail of evaluated offending drugs and their ADE's due to ADRs, drug interactions and Medication errors are depicted in ***table 3.***

Discussion

Impicciatore & Mucci, 2010 (3) reported that ADR case report lack important information particularly published in non specialised journals. 11% of the reports included the proprietary name while duration, dosage, route and formulation were reported in 87%, 85%, 37% and 21% of the reports, respectively.99% & 97% of reports provide management outcome and information regarding diagnostic tests and 52% cases gave information about seriousness of reactions. Causality assessment was reported in 81%, and rating scales to support the causal link were used in 20% of the reports.

The results of the current study are partially in agreement to the above study in some aspects whereas, they showed discrepancy in others. In our study 98.95% of ADE provided information about drug dosage, duration and route. Where with non proprietary names were provided in 100% of the cases. Outcome of the reaction was given in 98.95% of the cases. Relevant Laboratory investigations were present in 76.04% of the cases, present but inadequate in 19.79% of the cases. In current study Naranjo Scale was not used in 21.88% of cases unlike the above mentioned study. While as severity scale was not applied in 90.63% of the cases like above mentioned study.

Esteban Calvo C *et al.* 2008 (6) , in their study reported that the data elements were more often incomplete regarding dose, length of treatment, as well as length of adverse reaction. Only one third of the published case reports included full information.

Sempere E *et al*, 2006 (7) documented that there were no differences in the mean minimum publication criteria in their study. The causal relationship was acceptable; the documentation quality was high, with few unknown

Table 1. ADR profile of Published Reports

Total ADE Evaluated	96	**Statistical Values**
Classification of ADE		
Drug Itself	*83(86.45%)*	Chi square=184.03
Drug-Drug Interaction	*10(10.41%)*	DF=2
Medication Error	*3(3.13%)*	P value=0.0001
Seriousness of Reaction		
Others	*44(45.83%)*	Chi square=148.14
Hospitalization (Initial or Prolonged)	*30(31.25%)(Initial – 26.04%;*	DF=6
Life Threatening	*Prolonged – 5.21%)*	P value=0.0001
Death	*14(14.58 %)*	
Disability	*4(4.17%)*	
Required Intervention To Prevent	*3(3.13%)*	
Permanent Damage	*1(1.04%)*	
Congenital Anomaly	*0(0%)*	
Outcome of Reaction		
Recovered	*75(78.95%)*	Chi square=315.3
Recovering	*8(8.42%)*	DF=5
Fatal	*4(4.21%)*	P value=0.0001
Others	*5(5.20%)*	
Continuing	*3(3.16%)*	
Unknown	*1(1.05%)*	
Type of Reaction		
A	14(14.5%)	Chi square=205
B	19(19.7%)	DF=5
C	2(2.08%)	P value=0.0001
D	0(0%)	
E	0(0%)	
Unclassified	61(63.5%)	
ADE Due to		
Previously used Drugs	*75(78.12%)*	Chi square=60.75
Recently Introduced Drugs	*21(22.91%)*	DF=1
		P value=0.0001

reactions and ADRs to recently marketed drugs. Relevance was generally low, although greater in Medicina Clínica. The results of our study are not in agreement with this study. Similar scenario like our study was reported by Kelly WN, 2003 (8) in a descriptive analysis of 1520 ADE case reports published in English journal over a 20-year period and suggested that patient variables were reported >90% of the time. Most of the relevant ADE variables were reported most often. Added information for drug interactions, medication errors, and allergic drug reactions were reported 61-99% of the time. Less than 1% of ADE reporters objectively assessed the probability of the ADE.

The possible reasons for variations from current study might be due to journal with variable impact factors and indexing status as well countries from where they are published. In the current study Naranjo and WHO scale, severity scale and preventability scale were not applied in majority. The application of these scales is utmost important to quantify severity possibility of its prevention and possibility of its likelihood due to the drug. Non clarity of temporal relationship in some of the cases reduces the possibility of reaction happening due to offending drug. Similarly, inadequacy of medical contents of the report may not prove useful for educational purposes at individual levels to enhance drug safety & improve clinical practice.

In majority of the published case reports dose response relationship was not seen thereby resulting in difficulty to categorise type of ADR. The data was not reported according to the PvPI - SOP in majority of the cases. This point towards the tendency of reporter to publish directly bypassing, PvPI for personal academic interests. Which can delay the signal. (9) In the present study pictorial evidence was not documented in a large number of the cases whereas; only 6.25% cases did not require them. The pictorial evidence is always expected to enhance the authenticity of the published report and thus should always be encouraged. Drug estimation level was not done in majority of the cases and good number of the cases lacked relevant investigations and where these were done ,most of them were inadequate. These observations point towards poor authenticity of published reports. Other offending drug or pathology which could have contributed to the ADE was present in only 53.13% cases. This can grossly affect the WHO/UMC scale. There are guidelines like CARE guidelines that recommend to focuses the primary items like title, key words, abstract, introduction, patient information, clinical

Table 2. Critical Analysis of Published Reports

Total ADE's Evaluated	96	**Statistical Values**
Drug dosage, duration, route and formulation Provided	95 (98.95%)	
Non Proprietary names Provided	96(100%)	
Rationale of Publishing Case Report (Mentioned/Not Mentioned) Rare/ Unusual/ Usual/ Not Mentioned	*64(66.67%)/ 24(25.00%)/ 8(8.33%) /0(*0%)	Chi square=135.1 DF=3 P=0.0001
Naranjo Scale Probable / Not Used/ Definite/ Possible	64(66.66%)/ 21(21.88%)/ 7(7.29%)/4(4.17%)	Chi square=127.66 DF=3 P=0.0001
WHO/UMC Scale Not Used/ Probable/ Certain/ Possible	54(56.25%)/ 34(35.42%)/ 5(5.21%)/ 3(3.13%)	Chi square=100.11 DF=3 P=0.0001
Severity Scale Not Applied/ Applied	87(90.63%)/ 9(9.38%)	Chi square=126.75 DF=1 P=0.0001
Temporal Relation Clear/Not Clear	92(95.83%)/ 4(4.21%)	Chi square=161 DF=1 P=0.0001
Preventability Scale Not Applied/ Applied	91(94.79%)/ 5(5.21%)	Chi square=154.083 DF=1 P=0.0001
Medical Contents Of Report Adequate/ Inadequate	55(57.29%)/ 41(42.71%)	Chi square=4.083 DF=1 P=0.04331
Detail About Management of ADR Clear/ Not Clear	86(89.58%)/ 10(10.42%)	Chi square=120.3 DF=1 P=0.0001
Possible Hypothesis Clear/ Not Clear	90(93.75%)/ 6(6.25%)	Chi square=147 DF=1 P=0.0001
Dose Response Relationship(Treatment Schedule) Not Studied/ Studied	80(83.33%)/ 16(16.67%)	Chi square=85.3 DF=1 P=0.0001
SOP of PvPI Followed No/ Yes	89(92.71%)/ 7(7.29%)	Chi square=140.08 DF=1 P=0.0001
Pictorial Evidence Not Present/ Present/ Not Required	47(48.9%)/ 43(43.75%)/6(6.25%)	Chi square=47.92 DF=2 P=0.0001
Drug Level Estimation Not Done/ Done	89(92.71%)/ 7(7.29%)	Chi square=140.08 DF=1 P=0.0001
Any Other Offending Drug/Chemical/Pathology Present/ Not Present	51(53.13%)/ 45(46.88%)	Chi square=0.75 DF=1 P=0.0386
Clarity About Rechallenge/Dechallenge		Chi square=404.4 DF=4 P=0.0001
De-challenge Done	87(90.62%)	
De-challenge Not Done	5(5.20%)	
De-challenge not applicable	4(4.1%)	
Re-challenge Done	12(12.5%)	
Re-challenge not done due to ethical reasons	7(7.2%)	
Rechallenge not mentioned	63(65.6%)	
Rechallenge not done but mentioned	10(10.4%)	
Rechallenge not applicable	4(4.1%)	
Relevant Lab Investigations Present Present/ Present But Inadequate/ Not Present/ Not Applicable	73(76.04%)/ 19(19.79%)/3(3.13%) /1(1.04%)	Chi square=188.6 DF=3 P=0.0001

findings, timeline, diagnostic assessment, therapeutic interventions, follow-up and outcomes, discussion, patient perspective and informed consent. Whereas the Joint recommendations /guidelines of the (ISPE) & (ISoP) beside emphasising to focus on detail medical contents of report also implore to seek enough details for either a differential diagnosis or provisional assessment of cause-effect association, or a reasonable pharmacological or biological explanation. The results of the current study strongly points out that the inadequacies in these published ADR reports. To address this problem a multi-prong approach is a need of hour to improve the quality of ADR related case reports. Professional journals need to follow strict requirements for publishing ADE reports as per existing guidelines. There is a need to create awareness among the reporters that shall go long way to improve

Table 3. List of Published Offending drug and their respective ADE's

Adverse Drug Events (n=83) Clopidogrel- Exacerbation of Psoriasis; Bevacizumab- Necrotising Fascitis;(2)Metronidazole- Steven Johnson Syndrome+Neurological Symptoms, Cerebellar Ataxia; Mirtazapine- Hyponatremia/ Delerium; (3)Dapsone- Livedo Reticularis,Pancreatitis,Hypersensitivity Syndrome;(3)Olanzapine- Restless Leg Syndrome,Reversible Sensory Neural Hearing Loss, Neuroleptic Malignant Syndrome; Peg-Interferon & Ribavarin-Concurrent Interstitial Pneumonia & Pulmonary Embolism; Docetaxel- Palmoplantar Erythrodysesthesia Syndrome; Lorazepam- Diplopia; Tenofovir- Renal Failure; Piroxicam- Exanthemous Pustulosis; Sorafenib- Hand Foot Syndrome; Rivaroxaban- Rectus Sheath Haematoma; Levitiracetam- Acute Psychosis; Atorvastatin- Acute Hepatic Injury, Clinidipine- Ankle Oedema; (2)Ranitidine- Symetrical Drug Related Intertriginous & Flexural Exanthema,Anaphylaxis; Adalimumab- Factor 11 Deficiency; Rabeprazole + Diclofenac- Gastrointestinal Bleed; Thalidomide- Steven Johnson Syndrome + Toxic epidermal Necrolysis; (3)Carbamezepine- (2)Anticonvulsant Hypersensitivity Syndrome,Neutrophilic Eccrine Hidradenitis; Venlafaxine- Akathisia;Multiple suspected Drugs (Olmesartan/Perindopril/Torsemide)- Periodic Paralysis; Frusemide- Oligohydramnios; Isoniazid- Aloplecia; (2)Itraconazole- Skin Rash,Heart Failure; Bortezomib- Tumor Lysis Syndrome; Chlorpromazine- Tinnitus; Netilmycin- Carpopedal Spasm; Telmisartan+ Ramipril- Angioedema; Zoledronate- Acute Delirium; Bimatoprost Eye Drops- Hirsutism; (3)Ceftriaxone- Leucocytoclastic Vasculitis,Hypersensitivity Mimicking Measles,Haemolysis; Eslicarbezepine- Erythema Multiforme; Oyster Shell Calcium- Parotid Swelling; Acitretin- Pseudotumor Cerebri; Iron Sucrose- Anaphylaxis; Zotepine- Convulsive Seizures; (3)Sodium Valproate- Hair Loss,Enuresis,Priapism; Ofloxacin- Hallucination; Aripiprazole- Worsens Psychosis; Clofazimine- Enteropathy; Olmesartan- Maculopapular Rash; Deferasirox- Perforated Duodenal Ulcer; Lamivudine- Skin Rash; Moxifloxacin- Hypoglycemia; Oral Contraceptive Pill- Peripheral Arterial Disease; Fenofibrate- Rhabdomyolysis with Renal Failure; Domperidone- Galactorrhea; Nevaripine- Dress Syndrome; Terlipressin- Hyponatremic Seizure; Rifampicin & Pyrazinamide- Thrombocytopenia; Topical Diclofenac- Photosensitivity; Pregabalin-Drug Hypersensitivity Syndrome; Fluvoxamine- Oculogyric Dytonia & Mania; Allopurinol- Erythroderma; Methotrexate- Potts Disease+Hypercalcemia; Imatinib- Erythroderma; Phenytoin- Cerebellar Atrophy; Pregabalin- Self Harm Behaviour; Aceclofenac- Steven Johnson Syndrome/Toxic Epidermal Necrolysis; Clozapine- Thrombocytopenia; Allopurinol- Granuloma Annulare; Diclofenac- Acute Renal Failure; Multiple suspected Antipsychotics(Risperidone/Olanzapine/Trifluperazine/Quetiapine)- Pseudocyesis; Natalizumab- Suicide; Ethambutol- Pulmonary Eosinophilia
Adverse Drug Events due to Drug Interactions (n=10) Olanzapine+Escitalopram- Hyponatremia (PD); Duloxetine + Trichlormethiazide- Hyponatremia (PD); Netilmycin+ Ceftriaxone- Carpopedal Spasm (PD); Risperidone+Carbamezepine- Mania; Gancilovir+Tenofovir- Nephrotoxicity (PD); Tenofovir+ Ritonavir- Fanconi Syndrome (PK); Cefuroxime+Alcohol- Death[Disulfiram Like Reaction.](PK); Levofloxacin+Furazolidone-Toxic Epidermal Necrolysis (PD); Phenytoin + Cefepime- Steven Johnson Syndrome Exacerbation (PD); Ciclosporin+Voriconazole- Leucoencephalopathy (PK)
Adverse Drug Events Due to Medication Errors (n= 3) Ranolazine & Clarithromycin-Neurological Adverse Effect; Carbamezepine –Hypoglycemia; Methotrexate- Inflamed Psoriatic Plaque

the quality of reports. It is even more important because a poorly documented ADR reports with inadequate medical contents are likely to fail in their purpose.

Conclusion

The current underscores that the quality of published ADR reports in Indian Journals need to be improved in various aspects like WHO causality assessment, severity and preventability scale, pictorial documentation, laboratory evidences, temporal relationship, rationality and medical contents.

References

1. Gagnier JJ, Kienle G, Altman DG, *et al*. The CARE guidelines: consensus-based clinical case report guideline development. *J Clin Epidemiol* 2014;67(1):46-51.
2. Kelly WN, Arellano FM, Barnes J, *et al*. Guidelines for submitting adverse event reports for publication. *Drug Saf* 2007;30(5):367-73.
3. Impicciatore P, Mucci M. Completeness of published case reports on suspected adverse drug reactions: evaluation of 100 reports from a company safety database. *Drug Saf* 2010; 33(9):765-73.
4. Rehan HS, Chopra D, Holani SN, Mishra R. An observational study to compare the contents and quality of information furnished in CDSCO ADR reporting form, yellow card, medwatch and blue form by the healthcare professionals. *Int J Risk Saf Med* 2014; 26(1):1-8.
5. WHO Upalsa Monitoring Centre. Documentation Grading - Completeness Score. Available at: http://ipc.nic.in/writereaddata/mainlinkFile/File252.pdf Serial Online: 2014; Cited on: Jan 2015.
6. Esteban Calvo C, Ibáñez Ruiz C, Salgueiro Vázquez E, Manso Rodríguez G. [Impact of the spanish pharmacovigilance system recommendations on the publication of cases of adverse drug reaction]. *Aten Primaria* 2008; 40(11):555-8.
7. Sempere E1, Palop V, Bayón A, Sorando R, Martínez-Mir I. [Quality of the publication of adverse drug reactions in the letters to the editor section of four Spanish internal medicine and general medicine journals]. *Aten Primaria* 2006 15;37(4):187-92
8. Kelly WN. The quality of published adverse drug event reports. *Ann Pharmacother* 2003; 37(12):1774 8.
9. Tandon VR, Mahajan V, Khajuria V, Gillani Z. Underreporting of Adverse Drug Reaction a Challenge to Pharmacovigilance Programme of India (PvPI). *Ind J Pharmacol* 2015; 4(1): 65-71