ejpmr, 2016,3(3), 45-50

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

WHY THERE IS A NEED FOR DRUG POST MARKETING SURVEILLANCE?

Sundos Qassim[1*], Zakia Metwali[2] and Yassin Al Hariri[1]

[1]Clinical Pharmacy and Pharmacy Practice Department, Pharmacy College, Ajman University of Science and Technology, Ajman, United Arab Emirates.

[2]Pharmacology and Microbiology Department. Pharmacy College, Ajman University of Science and Technology, Ajman, United Arab Emirates.

***Author for Correspondence: Sundos Qassim**

Clinical Pharmacy and Pharmacy Practice Department, Pharmacy College, Ajman University of Science and Technology, Ajman, United Arab Emirates.

Article Received on 04/01/2016 **Article Revised on 25/01/2016** **Article Accepted on 16/02/2016**

ABSTRACT

All drug regulatory authorities have great responsibilities in ensuring the safety in addition to the quality and efficacy for all marketed drugs. Data from pre-marketing studies of drugs ensure the quality and the efficacy but lack the power to detect rare adverse drug reactions (ADRs) or events with significant latency. In view of this, post marketing surveillance play a prominent role in monitoring safety profile of marketed drugs.

KEYWORDS: Pharmacovigilance, post marketing surveillance, Adverse drug reactions, spontaneous reporting, adverse drug events, World Health Organization (WHO).

INTRODUCTION

The world health organization(WHO) defines an adverse drug reaction (ADR) as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function (Lee & Thomas, 2003, Kongkaew et al. 2008).

American Society of Health-System Pharmacists (ASHP, 1995) defined a side effect as an expected, well-known reaction resulting in little or no change in patient management (e.g., drowsiness or dry mouth due to administration of certain antihistamines or nausea associated with the use of antineoplastic). Another definition for the side effect by ASHP, that it is as an effect with a predictable frequency and an effect whose intensity and occurrence are related to the size of the dose (ASHP, 1995). Furthermore, drug withdrawal, drug-abuse syndromes, accidental poisoning, and drug-overdose complications should not be considered as ADRs (ASHP, 1995, Wiffen et al. 2002).

Medication errors (MEs) defined by the United States of America Institute of Medicines (IOM) as any errors occurring in the medication use process (ASHP, 1995, Nebeker et al. 2004). Wrong dosage administration or Wrong dosage prescribing are examples of MEs (ASHP, 1995, Wiffen et al. 2002, Mirzaee et al. 2015).

An adverse drug event (ADE) is"any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with treatment" (Glossary of Terms Used in Pharmacovigilance, 2011). Table (1).

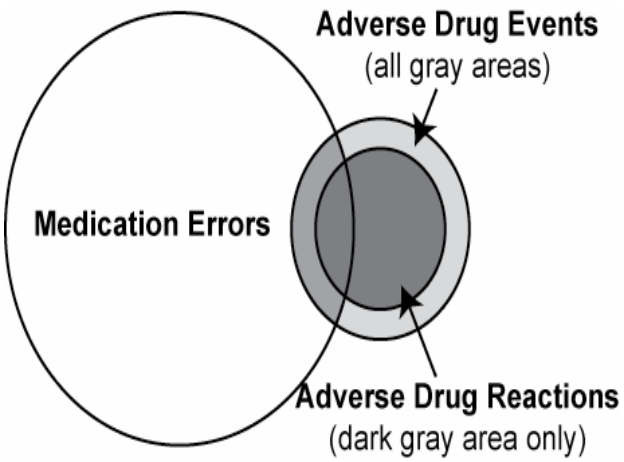

Figure 1: ADE ≠ Medication Errors (Nebeker et al. 2004).

Table 1: Summary of Definitions Relevant to Drug- Related Harm. (Nebeker et al. 2004)

Term	Definition	Example
Harm Occurred		
Adverse event	Harm in patient administered a drug but not necessarily caused by a drug	Traumatic death while taking lovastatin
Adverse drug reaction	Harm directly caused by a drug at a normal dosses -Unexpected adverse drug reaction -An adverse drug event whose nature or severity is not consistent with the product information	Congestive heart failure from metoprolol
Adverse drug event	Harm caused by the use of a drug -Harm caused by a drug or the inappropriate use of a drug	Hematoma from tirofiban overdose
Harm may have occurred		
Medication error	Inappropriate use of a drug that may or may not result in harm	Failure to renew prednisone order on transfer to medical ward
Side effect	A usually predictable or dose-dependent effect of a drug that is not principle effect for which the drug chosen; the side effect may be desirable, undesirable or inconsequential	
Harm did not occur		
Rational adverse drug event	Circumstances that could result in harm by the use of a drug but did not harm the patient	Receipt of roommates felodipine but no resulting hypotension

Table 2: ADE Severity categories classification (Morimto et al. 2004)

Types	Definition and Examples
Fatal	**Patient died due to the incident**
Life threatening	**Causes permanent damage or requires patient transferred to ICU** Haemorrhage with associated hypotension Hypoglycaemic encephalopathy Profound hypernatremia Acute renal failure requiring hospitalization Respiration failure requiring intubation Mental status change: patient falls and gets intracranial haemorrhage Tongue swelling/anaphylactic shock due to medication
Serious	**Requiring hospital admission, change in therapy or specific treatment** Urticaria Fall with an association fracture Haemorrhage requiring transfusion or hospitalization but without hypotension Delirium Gastrointestinal bleeding Altered mental status/excessive sedation to medication Increased creatinine due to medication Decrease in blood pressure, patient feels light-headed Allergic reaction, Shaking, chills/fever
Significant	**Any significant event that is identified by the patient but not requiring a change in therapy** Non urticarial skin rash Fall without associated fracture Haemorrhage not requiring transfusion or transplantation Over sedation Diarrhoea due to antibiotics Thrombocytopenia due to histamine type 2 antagonist Nausea resulting from oral potassium Nausea and vomiting due to erythromycin

Adverse Drug Events Classification:

Some of the adverse drug events (ADEs) are non-preventable as they cannot be avoided (Nebeker et al. 2004, Aspden et al. 2006, Aljadhey et al. 2013). On the other hand, there are preventable ADEs which are due to MEs and can be avoided with more precaution during medication use process (Wiffen et al. 2002, Teoh et al, 2015). For more details about ADE severity classification see Table (2).

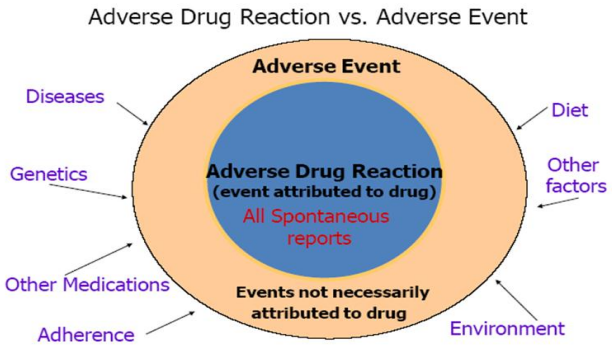

Figure 2: Relationship between ADRs and adverse event (AE) (Nebeker et al. 2004).

Adverse Drug Reactions Causality Assessment

Naranjo scale is used widely for the assessment of ADRs causality in order to determine whether an ADR is caused by drugs or other factors (Morimto et al. 2004, Gallagher et al. 2011). It is a questionnaire of 10 items that classifies the likelihood that a reaction is related to drug using variables like timing, plausibility / evidence, de-challenge and re-challenge/previous exposure (Gallagher et al. 2011). Each variable is weighed and the total score is used to categorise the event into unlikely, possible, probable and definite (Gallagher et al. 2011).

The Need for Pharmacovigilance

ADRs are one of the causing factors for hospital admission (Morimto et al. 2004, Nebeker et al. 2004, Hodgkinson et al. 2009, Mulatu & Worku, 2014, Perrone V et al. 2014, Qassim et al 2014a). It has been found that the incidence of ADRs induced hospital admissions is 5% to 6% of all medical admission (Gyllensten, et al. 2014, Mulatu & Worku, 2014).

ADRs are a cause of huge economic loss (Johnson and Bootman, 1996, Ayani et al. 1999, Dorman et al. 2000, Petal et al. 2007, Mulatu & Worku, 2014, Qassim et al. 2014b, Suyagh et al. 2015). The economic impact associated with medicine related mortality and morbidity is huge in which the cost exceeds the cost of the medication themselves (Smith, 1993, Wiffen et al. 2002, Suyagh et al. 2015). Although ADRs are causing a significant problem worldwide, large percentage of them are Preventable (Kanjanarat et al. 2003, Teoh et al, 2015).

Medicine safety studies conducted prior to introduction of new medicine into the market are very important to ensure drug safety, efficacy and to identify any ADRs related to the medicine. However, the numbers of patient evaluated in these studies are limited (Striker & Psaty, 2004, Kharkar & Bowalekar, 2012). People such as paediatric and geriatric are not included widely in clinical trials. Moreover, most of the safety and efficacy studies that identify ADRs are related to medicine used for short term and thus exclude the ability to recognize the ADRs resulting from long term use (Alastair, 2001, Kharkar & Bowalekar, 2012). Not all ADRs recognized from the early safety studies done by the manufacturer, so it is very important to monitor ADRs after marketing (Stricker & Psaty, 2004, Kharkar & Bowalekar, 2012).

In1960s, the tragedy of the thalidomide disaster has encouraged many countries for establishing screening systems for early observation and detection of ADRs (Meyboom et al. 1999, Qassim et al. 2014a). These systems are named as pharmacovigilance (PV) systems. WHO defined PV as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems" (ASHP, 1995, Mulatu & Worku, 2014, Ali & Irfan, 2015). PV is considered the core element for any medication safety study (Herdeiro et al. 2006, Ali and Irfan, 2015). PV is also named as post marketing surveillance as it plays a vital role in detecting any known and unknown ADRs of drugs available in the market (ASHP, 1995, Xie & Tian, 2013).

Fig 3: Thalidomide infants (vaccinetruth.org)

WHO International Program For Drug Safety Monitoring

In 1968 the WHO established an international program for drug safety monitoring with the participation of ten Countries (Mulatu & Worku,2014). and as of January 2016, 123 Countries have been joined the WHO Drug Monitoring Program as official members and in addition 28 associate members are awaiting full membership (WHO. int,2016).

VigiBase is managed and maintained by the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (Lindquist, M 2008). In October 2014, there were over 10 million reports of adverse reactions in Vigi Base. Data in VigiBase are recorded in a structured and comprehensive way to allow the detection of potential medicinal safety hazards.

In April 2015, WHO launched Vigi Access TM. Vigi Access is a new web application that will allow anyone to access information and encourage the reporting of adverse effects from medicinal products (Wallbergl, M. 2015).

Pharmacists Role in PV

Spontaneous reporting systems are of great importance in any PV system to gather information about ADRs (Mulatu &Worku, 2014, Obara et al. 2015, Rajiah et al. 2015). With such systems reporters submit ADRs reports on a voluntary basis and then the information entered onto a database for assessment and signal generating (Herdeiro et al. 2006, Pellegrino et al. 2013). In fact, spontaneous reporting is now regarded as the main mechanism of the PV system for identifying ADRs after the drug is released into the market (Edwards and Olsson, 2002, Obara et al. 2015, Rajiah et al. 2015). Spontaneous ADRs reporting is considered a major source of medicine safety data (Meyboom et al. 2002, Obara et al. 2015, Rajiah et al. 2015). It also, plays an active role in ensuring safe use of medicines and in minimizing the occurrence and the severity of ADRs (Hartigan, 2001, Sivanandy et al. 2013).

Establishing PV centre program is one of the best strategies for monitoring ADRs which in turn help in encouraging health care professionals to report suspected ADRs they may encounter in their clinical practice (Li et al. 2004, Qassim et al. 2014b). However, there is a low level of reporting for serious reactions are identified (WHO, 2002, Obara et al. 2015). One of the factors responsible for underreporting is the lack of the knowledge about reporting ADRs (Cosentino et al. 1997, Rehan et al. 2002, Lee and Thomas, 2003, Li et al. 2004, Oshikoya and Awobusuyi, 2009, Qassim et al. 2014a, Alraie et al. 2016,). Participation of all health care professional in reporting ADRs is the corner stone for a successful PV program (Al-Essa et al, 2015, Teoh et al, 2015, Tasaka et al. 2016). The Pharmacist as one of the health care professionals has immense responsibility in strengthening PV system (Faich, 1986, ASHP, 1995, Elkalmi et al. 2011, Qassim et al.2014a, Farha et al. 2015, Tasaka et al. 2016). The pharmacist is often the last member of the health care team to see the patient before the medicine is taken. The pharmacist can even educate the patient about signs and symptoms that should be reported immediately (Farha et al. 2015). Detecting, reporting and assessing any suspected ADRs is much a moral duty for the pharmacist as are other aspects of patients care (Van Grootheest et al. 2002, Sivanandy et al. 2013, Qassim et al.2014b, Obara et al. 2015, Rajiah, et al. 2015, Tasaka et al. 2016).

REFERENCES

1. Alastair, J.J.W. Adverse Reactions to Drugs In: Braunwald (ed). Harrisons principles of internal medicine. 15th edition. MC Graw-hill, 2001; 430-438.
2. Al-Essa, R. K., Al-Rubaie, M., Walker, S., & Salek, S. The Current Status of Drug Safety and Pharmacovigilance. In Pharmaceutical Regulatory Environment Springer International Publishing, 2015; 115-140.
3. Ali, I., Khan, A. U., & Irfan, I. U. Pharmacovigilance and pharmacists: Need for enhancing role as active health professionals. Archives of Pharmacy Practice, 2015; 6(4): 99.
4. Aljadhey, H., Mahmoud, M. A., Hassali, M. A., Alrasheedy, A., Alahmad, A., Saleem, F. & Bates, D. W. (2014). Challenges to and the future of medication safety in Saudi Arabia: A qualitative study. Saudi Pharmaceutical Journal, 2014; 22(4): 326-332.
5. Alraie, N. A., Saad, A. A., Sabry, N. A., & Farid, S. F. Adverse drug reactions reporting: a questionnaire-based study on Egyptian pharmacists' attitudes following an awareness workshop. Journal of evaluation in clinical practice, 2016.
6. American Society of Health-System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting. Am J Health-Syst Pharm, 1995; 52: 417–9.
7. Aspden, P., Wolcott, J., Bootman, J. L., & Cronenwett, L. R. (Eds.). Preventing medication errors: quality chasm series. National Academies Press, 2006.
8. Ayani, I., Aguirre, C., Gutierrez, G., Madariaga, A., Rodríguez-Sasiaín, J. M., & Martínez-Bengoechea, M. J. A cost-analysis of suspected adverse drug reactions in a hospital emergency ward. Pharmacoepidemiology and drug safety, 1999; 8(7): 529-534.
9. Classen, D.C., Pestotnil, S.L., Evans, R.S., Lioyd, J.F & Burke, J.P. Adverse drug events in hospitalized patients. JAMA, 1997; 277: 301-306.
10. Cosentino, M., Leoni, O., Banafi, F., Lecchini, S., & Frigo, G. Attitudes to adverse drug reaction reporting by medical practitioners in a Northern Italian district. Pharmacological research, 1997; 35(2): 85-88.

11. Dormann, H., Muth-Selbach, U., Krebs, S., Criegee-Rieck, M., Tegeder, I., Schneider, H. T., & Geisslinger, G. Incidence and costs of adverse drug reactions during hospitalisation. Drug safety, 2000; 22(2): 161-168.
12. Edwards, I.R. & Olsson, S. WHO Programme-Global Monitoring In: Mann RD and Andrews EB.Pharmacovigilance. John Wiley and Sons Ltd, 2002; 169-182.
13. Elkalmi, R. M., Hassali, M. A., Ibrahim, M. I. M., Widodo, R. T., Efan, Q. M., & Hadi, M. A. Pharmacy Students' Knowledge and Perceptions About Pharmacovigilance in Malaysian Public Universities. American journal of pharmaceutical education, 2011; 75(5).
14. Faich, G. A. Adverse-drug-reaction monitoring. The New England journal of medicine, 1986; 314(24): 1589.
15. Farha, R. A., Alsous, M., Elayeh, E., & Hattab, D. A Cross-Sectional Study on Knowledge and Perceptions of Pharmacovigilance among Pharmacy Students of Selected Tertiary Institutions in Jordan. Tropical Journal of Pharmaceutical Research, 2015; 14(10): 1899-1905.
16. Gallagher, R. M., Kirkham, J. J., Mason, J. R., Bird, K. A., Williamson, P. R., Nunn, A. J., & Pirmohamed, M. Development and inter-rater reliability of the Liverpool adverse drug reaction causality assessment tool. PloS one, 2011; 6(12): 28096.
17. Glossary of terms use in pharmacovigillance (2011) online (Assessed 1st November 2012). Available from World Wide Web http://who-umc.org/Graphics/24729.pdf.
18. Gyllensten, H., Hakkarainen, K. M., Hägg, S., Carlsten, A., Petzold, M., Rehnberg, C., & Jönsson, A. K. Economic impact of adverse drug events–a retrospective population-based cohort study of 4970 adults. PloS one, 2014; 9(3): 92061.
19. Hartigan-Go, K. Pharmacovigillnace and the pursuit of rational drug use.The Philippines experience, Uppsala Reports, 2001; 14: 1-4.
20. Herdeiro, M. T., Figueiras, A., Polónia, J., & Gestal-Otero, J. J. Influence of pharmacists' attitudes on adverse drug reaction reporting. Drug safety, 2006; 29(4): 331-340.
21. Hodgkinson, M. R., Dirnbauer, N. J., & Larmour, I. Identification of Adverse Drug Reactions Using the ICD-10 Australian Modification Clinical Coding Surveillance. Journal of Pharmacy Practice and Research, 2009; 39(1): 19.
22. Hughes, M. L., Whittlesea, C. M., & Luscombe, D. K. Review of national spontaneous reporting schemes. Adverse drug reactions and toxicological reviews, 2002; 21(4): 231-241.
23. Johnson, J. A., & Bootman, J. L. Drug-related morbidity and mortality: a cost-of-illness model. Archives of Internal Medicine, 1995; 155(18): 1949.
24. Kanjanarat, P., Winterstein, A. G., Johns, T. E., Hatton, R. C., Gonzalez-Rothi, R., & Segal, R. Nature of preventable adverse drug events in hospitals: a literature review. American Journal of Health-System Pharmacy, 2003; 60(17): 1750-1759.
25. Kharkar, M., & Bowalekar, S. Knowledge, attitude and perception/practices (KAP) of medical practitioners in India towards adverse drug reaction (ADR) reporting. Perspectives in clinical research, 2012; 3(3): 90.
26. Kongkaew, C., Noyce, P. R., & Ashcroft, D. M. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Annals of Pharmacotherapy, 2008; 42(7-8): 1017-1025.
27. Lee, A. & Thomas, S.H.L. Adverse drug reactions In: Walker R and Edward C. Clinical Pharmacy and Therapeutics. 3 rd edition Churchill Livigstone, 2003; 33-46.
28. Li, Q., Zhang, S. M., Chen, H. T., Fang, S.P., Yu, X., Liu, D., & Zeng, F. D. Awareness and attitudes of healthcare professionals in Wuhan, China to the reporting of adverse drug reactions. Chinese medical journal (English), 2004; 117(6): 856-861.
29. Lihite, R. J., & Lahkar, M. An update on the Pharmacovigilance Programme of India. Frontiers in pharmacology, 2015; 6.
30. Lindquist, M. VigiBase, the WHO global ICSR database system: basic facts. Drug Information Journal, 2008; 42(5): 409-419.
31. Meyboom, R. H., Egberts, A. C., Gribnau, F. W., & Hekster, Y. A. Pharmacovigilance in perspective. Drug Safety, 1999; 21(6): 429-447.
32. Mirzaee, H., Mostafaie, D., Estebsari, F., Bastani, P., Kalhor, R., & Tabatabaee, S. Medication Errors in Hospitals: A Study of Factors Affecting Nursing Reporting in a Selected Center Affiliated with Shahid Beheshti University of Medical Sciences. Journal of Pharmaceutical Care, 2015; 2(3): 96-102.
33. Morimoto, T., Gandhi, T. K., Seger, A. C., Hsieh, T. C., & Bates, D. W. Adverse drug events and medication errors: detection and classification methods. Quality and safety in health care, 2004; 13(4): 306-314.
34. Mulatu, W. N., & Worku, A. Assessment of Knowledge, Attitude and Practice of Health Professionals towards Adverse Drug Reaction Reporting and Factors Associated with Reporting. Journal of Pharmacovigilance, 2014.
35. Nebeker, J. R., Barach, P., & Samore, M. H. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Annals of internal medicine, 2004; 140(10): 795-801.
36. Obara, T., Yamaguchi, H., Satoh, M., Iida, Y., & Sakai, T. Prevalence, Determinants, and Reasons for the Non-Reporting of Adverse Drug Reactions by Pharmacists in the Miyagi and Hokkaido Regions of Japan. Adv Pharmacoepidemiol Drug Saf, 2015; 4(191): 2167-1052.
37. Oshikoya, K. A., & Awobusuyi, J. O. Perceptions of doctors to adverse drug reaction reporting in a

teaching hospital in Lagos, Nigeria. BMC Pharmacology and Toxicology, 2009; 9(1): 14.
38. Patel, K. J., Kedia, M. S., Bajpai, D., Mehta, S. S., Kshirsagar, N. A., & Gogtay, N. J. Evaluation of the prevalence and economic burden of adverse drug reactions presenting to the medical emergency department of a tertiary referral centre: a prospective study. BMC clinical pharmacology, 2007; 7(1): 8.
39. Pellegrino, P., Carnovale, C., Cattaneo, D., Perrone, V., Antoniazzi, S., Pozzi, M., & Radice, S. Pharmacovigilance knowledge in family paediatricians. A survey study in Italy. Health policy, 2013; 113(1): 216-220.
40. Perrone, V., Conti, V., Venegoni, M., Scotto, S., Degli Esposti, L., Sangiorgi, D., & Vighi, G. Seriousness, preventability, and burden impact of reported adverse drug reactions in Lombardy emergency departments: a retrospective 2-year characterization. ClinicoEconomics and outcomes research, 2014; 6: 505.
41. Qassim, S., Metwaly, Z., Shamsain, M., & Al Hariri, Y. Reporting adverse drug reactions: evaluation of knowledge, attitude and practice among community pharmacists in UAE. IOSR Journal of Pharmacy, 2014; 22(30): 31-40.
42. Qassim, S., Metwaly, Z., Shamsain, M., & AlHariri, Y. Spontaneous reporting of adverse drug reactions in UAE: obstacles and motivation among community pharmacists. International Journal of Pharmaceutical Sciences and Research, 2014; 5(10): 4203.
43. Rajiah, K., Maharajan, M. K., & Nair, S. Pharmacy students' knowledge and perceptions about adverse drug reactions reporting and pharmacovigilance. Saudi Pharmaceutical Journal, 2015.
44. Rehan, H. S., Vasudev, K., & Tripathi, C. D. Adverse drug reaction monitoring: knowledge, attitude and practices of medical students and prescribers. National Medical Journal of India, 2002; 15(1): 24-26.
45. Sivanandy, S., Kumaran, K. S. A., & Rajasekaran, A. Knowledge assessment in adverse drug reactions and reporting. Archives of Pharmacy Practice, 2013; 4(3): 104.
46. Smith, D. L. The effect of patient noncompliance on health care costs. Med Interface, 1993; 6(4): 74-6.
47. Stricker, B. H., & Psaty, B. M. Detection, verification, and quantification of adverse drug reactions. BMJ: British Medical Journal, 2004; 329(7456): 44.
48. Suyagh, M., Farah, D., & Farha, R. A. Pharmacist's knowledge, practice and attitudes toward pharmacovigilance and adverse drug reactions reporting process. Saudi Pharmaceutical Journal, 2015; 23(2): 147-153.
49. Tasaka, Y., Yasunaga, D., Tanaka, M., Tanaka, A., Asakawa, T., Horio, I., & Araki, H. Economic and safety benefits of pharmaceutical interventions by community and hospital pharmacists in Japan. International journal of clinical pharmacy, 2016; 1-9.
50. Teoh, B. C., Alrasheedy, A. A., Hassali, M. A., Tew, M. M., & Samsudin, M. A. Perceptions of Doctors and Pharmacists towards Medication Error Reporting and Prevention in Kedah, Malaysia: A Rasch Model Analysis. Adv Pharmacoepidemiol Drug Saf, 2015; 4(192): 2167-1052.
51. Tribino, G., Maldonado, C., Segura, O., & Díaz, J. Direct costs and clinical aspects of adverse drug reactions in patients admitted to a level 3 hospital internal medicine ward. Biomedica, 2006; 26(1): 31-41.
52. Vaccintruth, 2003, [online] Available at: < http://www.vaccinetruth.org/thalidomide. > [Accessed 1 February 2016].
53. Van Grootheest, A. C., Van Puijenbroek, E. P., & de Jong–van den Berg, L. T. W. Contribution of pharmacists to the reporting of adverse drug reactions. pharmacoepidemiology and drug safety, 2002; 11(3): 205-210.
54. Wallbergl, M. VigiAccess-e Public Key to The WHO ICSR Database. In DRUG SAFETY. THE WAREHOUSE WAY, NORTHCOTE 0627, AUCKLAND, NEW ZEALAND: ADIS INT LTD, 2015; 38(10): 1040-1040.
55. Wiffen, P., Gill, M., Edwards, J., & Moore, A. Adverse drug reactions in hospital patients: a systematic review of the prospective and retrospective studies. Bandolier Extra, 2002; 101(4).
56. wHO. Available from http://www.who.int/medicines/areas/quality_safety/safety_efficacy/National_PV_Centres_Map/en/ .Accessed : January, 1, 2016.
57. World Health Organization. The importance of pharmacovigilance: safety monitoring of medicinal products. Geneva: World Health Organization, 2002; 1-48.
58. Xie, Y. M., & Tian, F. Regulations and guidelines should be strengthened urgently for re-evaluation on post-marketing medicines in China. Chinese journal of integrative medicine, 2013; 19, 483-487.