WHY THERE IS A NEED FOR DRUG POST MARKETING SURVEILLANCE?

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

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harm Occurred</td>
<td>Harm in patient administered a drug but not necessarily caused by a drug</td>
<td>Traumatic death while taking lovastatin</td>
</tr>
<tr>
<td>Adverse event</td>
<td>Harm directly caused by a drug at a normal doses</td>
<td>Congestive heart failure from metoprolol</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>Unexpected adverse drug reaction</td>
<td></td>
</tr>
<tr>
<td>Adverse drug event</td>
<td>An adverse drug event whose nature or severity is not consistent with the product information</td>
<td>Hematoma from tirofiban overdose</td>
</tr>
<tr>
<td>Harm may have occurred</td>
<td>Inappropriate use of a drug that may or may not result in harm</td>
<td>Failure to renew prednisone order on transfer to medical ward</td>
</tr>
<tr>
<td>Side effect</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Harm did not occur</td>
<td>Circumstances that could result in harm by the use of a drug but did not harm the patient</td>
<td>Receipt of roommates felodipine but no resulting hypotension</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Types</th>
<th>Definition and Examples</th>
</tr>
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| Fatal               | 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 |
| Life threatening    | Requiring hospital admission, change in therapy or specific treatment                                                                                                                                           |
| Serious             | 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-heeded  
                      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).
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 (Morimoto 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 (Morimoto et al. 2004, Nebeker et al. 2004, Hodgkinson et al. 2009, Mulatu & Worku, 2014, Perrone V et al. 2014, Qassim et al. 2014). 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. 2014). 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).
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 (Wallberg, 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 ADR 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, Elkalami 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


37. Oshikoya, K. A., & Awobusuyi, J. O. Perceptions of doctors to adverse drug reaction reporting in a