UNIVERSITI TEKNOLOGI MARA

ANALYSIS OF ADVERSE DRUG REACTIONS RELATED TO DRUG-INDUCED RENAL INJURY BASED ON SPONTANEOUS ADVERSE DRUG REACTIONS REPORTING IN MALAYSIA 2010 - 2014

NURULMAYA BINTI AHMAD SA'AD

Master of Pharmacy Practice

January 2016

AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This dissertation has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

Name of Student : Nurulmaya Binti Ahmad Sa'ad

Student I.D. No. : 2014404624

Programme : Master of Pharmacy Practice

Faculty : Pharmacy

Dissertation Title : Analysis of adverse drug reactions related to drug-induced renal injury based on spontaneous adverse drug reactions reporting in Malaysia 2010 - 2014

Signature of Student :

Date : January 2016

CONFIRMATION BY PANEL OF EXAMINERS

I certify that a Panel of Examiners has met on 21st January 2016 to conduct the final examination of Nurulmaya Binti Ahmad Sa'ad on her Master of Pharmacy Practice dissertation entitled "Analysis of Adverse Drug Reactions Related to Drug-Induced Renal Injury Based on Spontaneous Adverse Drug Reactions Reporting in Malaysia 2010 - 2014" in accordance with Universiti Teknologi MARA Act 1976 (Akta 173). The Panel of Examiners recommends that the student be awarded the relevant degree. The Panel of Examiners was as follows:

Prof. Dr. Noorizan Bt. Abdul Aziz, PhD
Professor
Faculty of Pharmacy
Universiti Teknologi MARA
(Supervisor)

Dr Yogheswaran Gopalan, PhD
Lecturer
Faculty of Pharmacy
Universiti Teknologi MARA
(Internal Examiner)

Khairil Anuar Bin Md Isa,
Lecturer
Faculty of Health Science
Universiti Teknologi MARA
(External Examiner)

AISHAH BINTI ADAM, PhD
Professor
Dean
Faculty of Pharmacy
Universiti Teknologi MARA
Date: 18 February 2016

ABSTRACT

Background: In Malaysia, it has been reported that drug-induced renal injury is one of the top 10 types of adverse drug reactions (ADRs) reported in Malaysia. The incidence has increased throughout the year sand a closer view needs to be taken. To date, studies that investigate the nephrotoxicity based on the spontaneous ADR reporting database in Malaysia are very limited.
Objectives: To analyse the data on spontaneous ADR reports related to drug-induced renal injuries and urinary system disorders in Malaysia from 2010 to 2014. In addition, the aims of this study also to describe the pattern of drug-induced renal injury reported in Malaysia. This study also aimed to determine the predisposing factors that lead to drug-induced renal injury.
Methods: This is a retrospective study where the data was collected at Pharmacovigilance Section, Centre of Post Registration Product, National Pharmaceutical Control Bureau (NPCB). A total of 2093 ADR reports from 2010 to 2014 related to the renal disorders were extracted from the Quest 2 database, regardless of the seriousness. Reports were classified according to the World Health Organisation (WHO) criteria for causality assessment and the types of renal injury were determined according to system organ class (SOC) of urinary system disorders.
Results: From the results, it was found that 1.11 drugs were recorded per report. 52% percent of the patients with the studied ADRs were women and almost 49.5% of them were Malay. Patients between 46 to 60 years old were found to be highest group of patients reported with drug-induced renal injuries. It was found that there is no association between gender ($P = 0.181$), race ($P = 0.269$) and age groups ($P = 0.563$) and the extent of severity. 85.7% of the reports were classified as possible. Pearson chi square test showed that there is a strong association between concomitant drug groups and the extent of severity ($P < 0.001$). Most of cases were reported with sub-acute reaction and it was found that there is a strong association between onsets of time category and the extent of severity ($P = < 0.001$) where the latent onset of time has a higher occurrence of severe adverse reactions. Out of 1904 cases, face oedema was found to be at the top of the list with 60.8% of the reported cases. Diclofenac was found to be the most reported drug causing renal injuries. From the statistical analysis, it was found that the only variable which is dosage shows a significant association with the increase in the severity of reaction caused by diclofenac.
Conclusion: In conclusion, this study has pointed out diclofenac as the most common drug that causes reported renal injuries besides demonstrating the trend of renal injuries due to the use of diclofenac. Although diclofenac can be considered as safe and effective therapeutic NSAIDs for the management of a variety acute and chronic condition, it has to be used with justifiable caution. Healthcare professionals should be aware of the risk for diclofenac associated renal injuries and need to screen patients appropriately for impairment risk factors before commencing diclofenac therapy.

ACKNOWLEDGEMENT

Firstly, I wish to thank Allah for giving me the opportunity to embark on my Master and for completion of this long and challenging journey successfully. At the end of my thesis, I would like to thank all those people who made this thesis possible and an unforgettable experience for me. I would never have been able to finish my dissertation without the guidance of my supervisors, friends, and support from my husband and my family.

Here, I would like to express my deepest gratitude to my main supervisor, Prof. Dr. Noorizan Bt. Abdul Aziz, for her excellent guidance, caring, patience, and providing me with an excellent atmosphere for conducting research. I would also like to express my warmest appreciation to my field supervisor, Pn. Rokiah Bt. Isahak, Senior Principal Assisstant Director, Head of Pharmacovigilance Unit, Centre of Post-registration Products, National Pharmaceutical Control Bureau (NPCB) for providing me with the facilities, guidance, assistance and great ideas. A big thank also goes to the staff of Pharmacovigilance Unit, Centre of Post-registration Products, NPCB, for helping me with the data collection and extraction. Special thanks to classmates and friends for helping me with this project. My sincere thanks must also go to Mr Khairil Anuar Bin Md.Isa for his assistance and his teaching in interpreting the statistically analysed results.

Finally, this dissertation is dedicated to my loving family especially my husband and son for the vision and determination to encourage me with patience. Alhamdulillah.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitor
ADQI	Acute Dialysis Quality Initiative
ADR	Adverse drug reaction
AGS	American Geriatric Society
AKI	Acute kidney injury
AMG	Aminoglycoside
ARB	Angiotensin-receptor blocker
ARF	Acute renal failure
ASHP	American Society of Health-System Pharmacists
ATC	Anatomical therapeutic chemical
CKD	Chronic kidney disease
COX	Cyclooxygenase
CRC	Clinical Research Centre
DCA	Drug Control Authority
ESRD	End stage renal disease
FDA	Food Drug Administration
GP	General practitioner
HO	Housemen officer

antiHPT	antihypertensive
ICH	International Conference on Harmonization
K/DOQI	Kidney Disease Outcomes Quality Initiative
MADRAC	Malaysian Adverse Drug Reactions Advisory Committee
MO	Medical officer
MOH	Ministry of Health Malaysia
MREC	Malaysian Research and Ethics Committee
NMRR	National Medical Research Registry
NPCB	National Pharmaceutical Control Bureau
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-the-counter
PRP	Provisional Registered Pharmacist
RCT	Randomized controlled trial
SD	Standard deviation
SOC	System Organ Class
SPSS	Statistical Package for Social Science
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

In the 1960s, the thalidomide tragedy has opened the eyes of many healthcare stakeholders and became the catalyst to the beginnings of the scrupulous drug approval and monitoring systems in place at the United States Food and Drug Administration (FDA) today. This tragedy and other additional incidents such as adverse reactions towards a high intake of estrogen oral contraceptive pills at that time became one of the major reasons for the increasingly stringent requirements to document drug safety development and the establishment of spontaneous adverse drug reactions reporting system (L Aagaard & Hansen, 2009; Fintel, Samaras, & Carias, 2009). Year by year, the increased number of incidences or occurrences of unanticipated, serious and alarming adverse drug reactions (hereafter ADRs) has fascinated and drawn healthcare professionals and public attention. The spike in these cases has resulted in suspicion on the effectiveness and quality of drug surveillance systems. In his article, Horton (2004) discusses on a recent example of an ADR case that describes the scandal of cyclooxygenase-2 (COX-2) inhibitors which has resulted in the withdrawal of rofecoxib (Vioxx ®) from the United States (US) market in 2004 due to unexpected emergence of cardiovascular events (related to the drug). The case had really taken the world by surprise and grabbed the attention of many. There are also some other well- known ADR cases that were discovered postmarketing such as rosiglitazone (PPAR-γ-agonist). Rosiglitazone has been associated with an increased risk of myocardial infarction, vigabatrine and visual field defects, tolcapone and risk of liver toxicity (Ferner & Butt, 2008; Stefan, Bernatik, & Knorr, 1999; Watkins, 2000). The growing number of incidences of ADR cases after the marketing of medicines, either serious or not, has raised an important question, to what extent do the existing systems and methods are effective in predicting the occurrence of ADRs (Lise Aagaard, Soendergaard, Andersen, Kampmann, & Hansen, 2007). Usually, a new medicine's information on the ADR profile progresses from observations conducted during the clinical development process. As we all

know, the gold standard for the study design is randomised controlled trials (RCTs) (Hansen, 1990). However, RCTs were designed to focus more on measuring the efficacy of the drug and not detecting the ADRs as the outcome. Due to some characteristics of RCT design such as short periods of investigation, a small number of carefully determined participants in the trial, fixed drug doses, and controlled conditions and environment, a narrow limit was set for the detection of information about serious and unanticipated ADRs (Bisson, Gross, Miller, & Weller, 2003; Hansen, 1990, 1992). The data on common side effects, easily noticeable ADRs can be detected in RCTs. However, unfamiliar long term adverse reactions are hardly visible. Those unknown and rare ADRs can be detected through other pharmacovigilance research designs such as spontaneous reporting systems, case-control studies and cohort studies. This study is conducted to analyse the ADR data specifically related to drug-induced renal injuries in Malaysia based on the spontaneous ADR reports to National Pharmaceutical Control Bureau (hereafter NPCB).

1.2 Problem Statement

Declining renal function among patients who received drugs is a common cause of renal injuries. Drugs caused approximately twenty percent (20%) of community and hospital acquired episodes of acute renal failure (Bellomo, 2006). In Malaysia, it has been reported that drug-induced renal injury is one of the top ten (10) types of ADR reported in Malaysia. Based on 2014's report ("Official Portal National Pharmaceutical Control Bureau," 2014), from the total of 11,921 ADR reports, 586 reports are related to urinary system disorders, which placed it as the 7th most reported ADR based on the system organ class in Malaysia (Figure 1.1). On the other hand, in 2013, the reported ADR related to this organ system was 507 and it was in the 8th place (8th ranked) of the most reported ADR in Malaysia (Figure 1.2). The ranking has changed as it went up one place from 2013 to 2014. This shows that the incidence has increased and a closer view needs to be taken. To date, limited studies have been done to investigate the nephrotoxicity based on the spontaneous ADR reporting database in Malaysia.

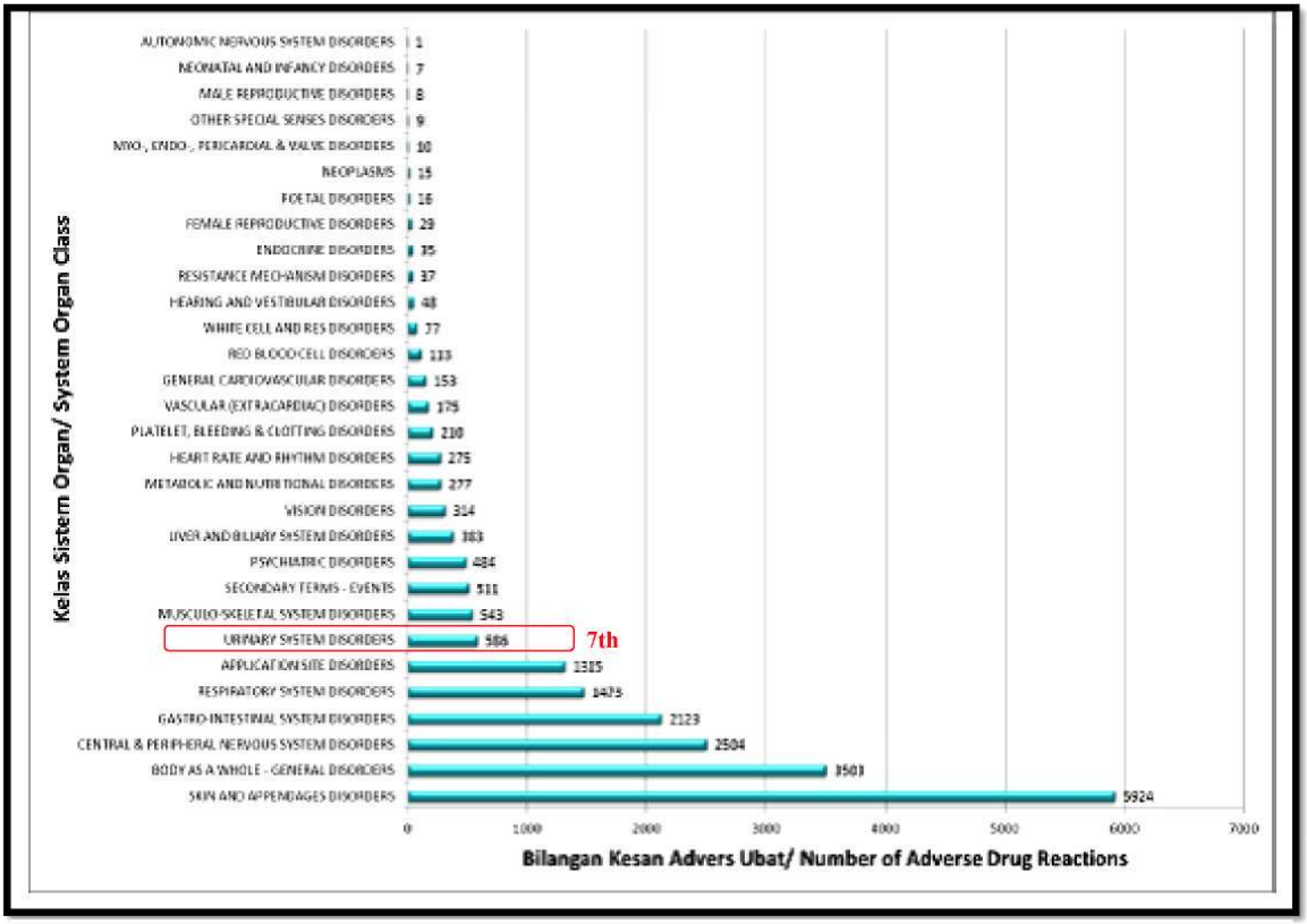


Figure 1.1: Number of Adverse Drug Reactions by System Organ Class (2014)

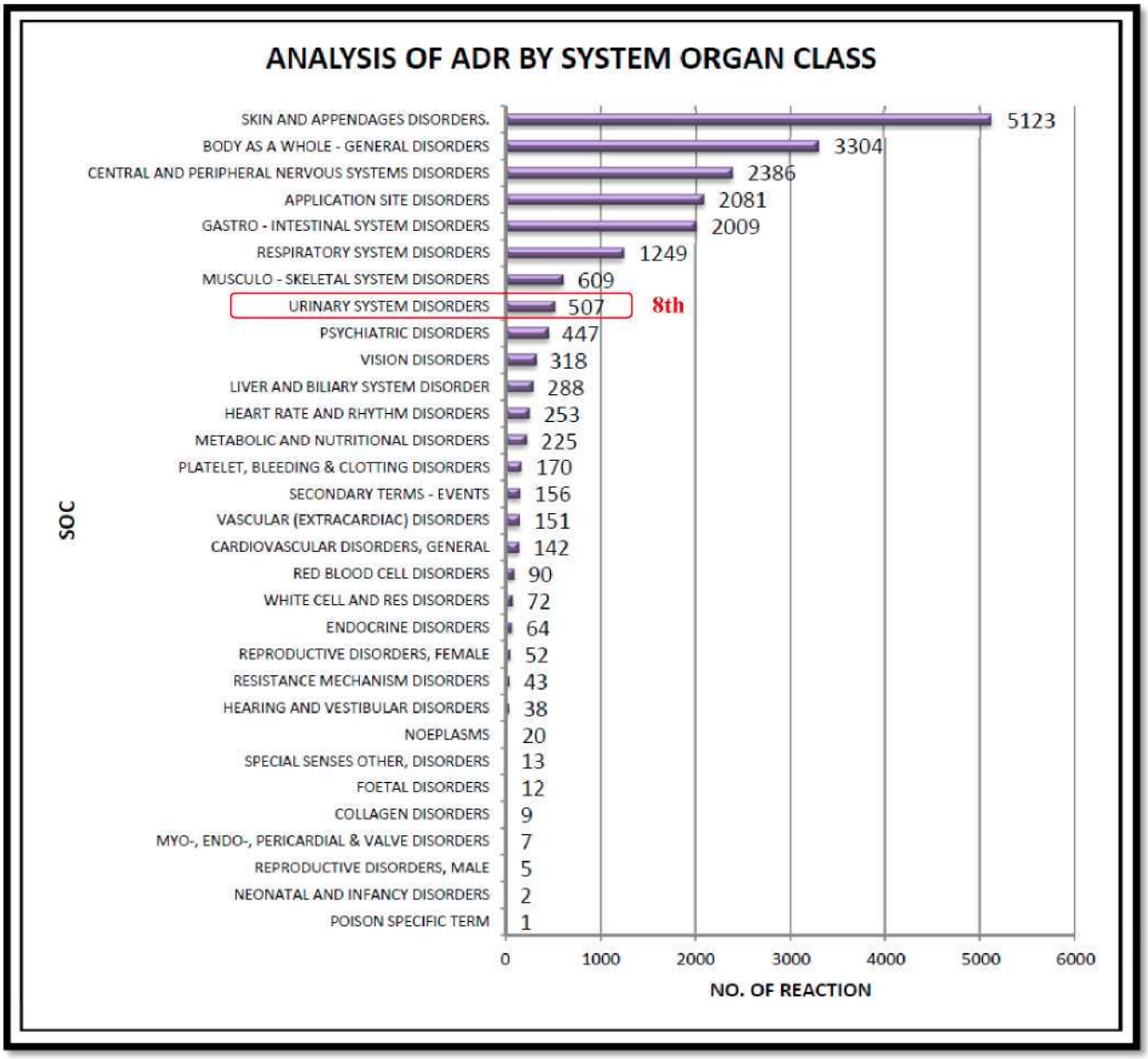


Figure 1.2: Number of Adverse Drug Reactions by System Organ Class (2013)

1.3 Research Objectives

1.3.1 General Objective

To analyse the data on spontaneous adverse drug reactions reports related to drug-induced renal injuries and urinary system disorders in Malaysia from 2010 to 2014

1.3.2 Specific Objectives

There are four main specific objectives in this study which are:

a) To describe the pattern / trend of adverse drug reaction related to drug-induced renal injuries spontaneously reported in Malaysia
b) To identify the most common drug or the highest usage of drug that cause renal injuries to describe a relevant pattern of the reported adverse reactions
c) To identify the predisposing factors/predictors which are susceptible to drug-induced renal injuries
d) To explore potential preventive measure to prevent drug-induced renal injuries

1.4 Research Question

What is the most common drug that causes renal injuries to patients and what are the predisposing factors/predictors of drug induced renal injuries reported in Malaysia?

1.5 Statistical Hypothesis

For this study, there are five null hypotheses that will be tested. They are:

a) There is no association between the extent of renal injury and gender.
b) There is no association between the extent of renal injury and race.
c) There is no association between the extent of renal injury and groups of age.
d) There is no association between the extent of renal injury and concomitant drugs.
e) There is no association between the extent of renal injury and onset of reaction.

1.6 Significance of the Study

From this study, we will be able to identify the most common reported drug that causes renal injuries. Besides that, we will also be able to correlate and observe the relationship between the drug, predictors and the adverse event to be studied.

1.7 Limitations of the Study

There are certain limitations of this study that may influence the findings. The limitations that need to be considered in this study are as follows:

a) Underreporting of data is possible as the data that will be collected are based on spontaneous adverse drug reporting – a passive method of ADR monitoring. There is no denominator to be compared to.
b) The low quality of ADR reports may cause inadequate information and may have to be omitted from the analysis and may affect the results. The low quality of ADR reports may lead to the inability to draw a conclusion to drug-induced renal injury. Furthermore, variations in reports may cause a discrepancy in captured data and may result in inappropriate causality assessment. Incomplete data such as information about de-

challenge re-challenge, onset of ADRs, dose, co-morbid disease and patient's medical history may complicate the analysis process. According to Perucca & Gilliam (2012), in population setting with natural and uncontrolled environment, it is hard to establish causality especially relevant information is missing or incomplete such as relation with dose, reversibility after drug discontinuation, and the effect of re-challenge or de-challenge.

1.8 Rationale of the Study

Postmarketing surveillance on the effects of drugs in clinical practice is indispensable. Therefore, spontaneous reporting of ADRs is essential as it increases the knowledge of drug safety (Wyswski & Swartz, 2005). The data on collected spontaneous reporting can then be used in research, inferential statistics and evaluation of the quality of healthcare.

The rationale of this study is to look into the developed renal problem due to the intake of drugs in Malaysia. By conducting this study, we can identify the prevalence of intended ADR and take precautions in order to prevent further episode and reduce the risk of the occurrence of drug-induced renal injuries. As stated by Cereza et al. (2010), the detection and evaluation of ADRs are required to increase the possibility of early identification of severe reactions, reactions of new drugs, increased frequency of known reactions, unknown effects, identification of the risk factors and possible dissemination of information among clinicians and health professionals. Through this study, it is hoped that preventive measures can be discovered and adopted by healthcare professionals while using the most common reported drug that causes renal problems. Drug-induced nephrotoxicity tends to be more common among certain patients and in specific clinical situations. Therefore, successful prevention requires comprehensive knowledge of pathogenic mechanisms of renal injury, patient-related risk factors, drug-related risk factors, and preemptive measures, coupled with vigilance and early intervention (Naughton, 2008).

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

In recent days, adverse drug reactions (ADRs) are a common and often preventable cause of hospital admission and in-hospital morbidity. ADRs have becoming an important challenge in today's modern medicine in terms of early recognition, proper management and avoid offensive practice. Adverse drug reactions can occur at any point of care in all settings where health care is offered and provided.

As defined by World Health Organization (WHO, 1972), an ADR is known as "*a response to a drug that is noxious and unintended and which occurs in doses normally used for the treatment, prophylaxis, or diagnosis of disease or the modification of physiological functio*n". It is an unwanted effect experienced by patients or consumers who consume medicine (or combination of medicines) under normal setting of use. The emerged reactions could be a well - known side effects or it could be a new and undetected beforehand. Side effect is defined by American Society of Health-System Pharmacists or ASHP (1995) as "*an expected, well-known reaction resulting in little or no change in patient management. The examples of side effects are drowsiness or dry mouth due to administration of certain antihistamines, nausea associated with the use of antineoplastics or constipation due to the consumption of opiates. ASHP further defines side effect as 'an effect with a predictable frequency and an effect whose intensity and occurrence are related to the size of the dose"*. Although such effects can be mild, they can also be serious and life-threatening. Side effects occur and presented as other than the intended therapeutic effect, whether beneficial, neutral or harmful. The term is sometimes considered synonymous with ADR, and is sometimes used to describe 'minor' and predictable ADRs. In addition, accidental poisoning, drug-abuse syndromes, drug withdrawal, and drug-over-dose complications should not be defined as ADRs. They may be regarded as adverse events. According to FDA, an adverse event is any undesirable experience associated with the use of a medical product in a patient ("Reporting Serious Problems to FDA - What is a Serious Adverse

Event?," 2014). Adverse event occurs while a patient is taking a drug and it is not necessary to determine whether the event was a response to the drug (Ferner & Butt, 2008). Adverse event may occur due to the devices or practices while the patient is given a drug.

Adverse drug reactions can be categorised into several types of reactions. Based on the proposal of Rawlins and Thompson (1977), type A and type B of ADRs occur on the basis of the mechanism of action (Aronson & Ferner, 2003). Type A (augmented) reactions is common and related to the drug's pharmacological actions when given at the usual therapeutic dose and are normally dose-dependent. It is predictable from the known pharmacology of the drug. They are basically less severe and occur more frequently than type B events and are usually detected at some point in the clinical trials before the drugs are being marketed. An example is the anticholinergic effects which are associated with tricyclic antidepressants. On the contrary, Type B (bizarre) reactions are not due to an extension of the known active pharmacologic properties of the drug and are non-dose related. They are pharmacologically unexpected, unpredictable, or idiosyncratic adverse reactions and thus termed as bizarre. They are less common and often can only be discovered for the first time after a drug has already been made available for general use. An example is skin rashes which are caused by antibiotics. Despite that, it is sometimes difficult to allocate a reaction to one type. For instance, dose dependent (type A) nausea and vomiting caused by consuming erythromycin can also be categorised as type B as it is not pharmacologically predictable.

J. K. Aronson (2002) has extended the classification to other alphabetically marked types to type C (dose and time dependent (chronic) reactions), type D (delayed reactions), type E (withdrawal reactions), and type F (failure of therapy). Types C, D, and E are not mechanisms but characteristics of their manifestations. Type C, or chronic reactions is related to the cumulative use of a drug. It has been suggested that Type C ADRs are connected with long-term drug therapies in which serious and common effects on public health takes place (Pirmohamed & Park, 2003; Rawlins & Thompson, 1977). An example of type C reaction is hypothalamic-pituitary-adrenal axis suppression by corticosteroids (Rohilla & Yadav, 2013) . Type D, or 'delayed' reactions, are time-related. The reaction becomes apparent sometime after the treatment. An example is teratogenesis e.g. vaginal adenocarcinoma with diethylstilbestrol and tardive dyskinesia caused by antipsychotic medication. Reactions which are associated with the

withdrawal of a medicine are known as Type E, or 'end-of-use' reactions. This type of reactions is known to emerge when the pharmacotherapy has been suddenly terminated and the best examples of this reaction are the withdrawal seizures on terminating anticonvulsant therapy and adrenocortical insufficiency following or as a subsequent to glucocorticoids termination. The last type is type F or 'failure' reactions which is often caused by drug interactions (Edwards & Aronson, 2000).

A meta-analysis by Lazarou, Pomeranz and Corey (1998) found that, on the whole, the incidence of serious ADRs in the general hospitalised population in the United States was 6.7%, whereas the incidence of fatal ADRs was 0.32% among the patients from thirty-nine (39) prospective studies (Lazarou et al., 1998). Other studies in Europe estimated that the percentage of ADRs that led to hospitalisation in general population varies from a bare minimum of 1.8% in Netherlands to 3.6% in Italy, 6.5% in Great Britain, 8.4% in Denmark to a maximum of 12.8% in Greece (Farcas et al., 2010). However, the percentages are even higher when it comes to the population of elderly which ranges from 8.4% to 24% (Olivier et al., 2009; Passarelli, Jacob-Filno, & Figueiras, 2005; Somers, Petrovic, Robays, & Bogaert, 2003). It is also apparent that ADRs may occur after the admission into the hospital which is reported to have been affecting up to 19.2% of the patients (Davies, Green, Mottram, & Pirmohamed, 2006; Lagnaoui, Moore, Fach, Longy-Boursier, & Begaud, 2000).

2.2 Overview of ADR reporting in Malaysia

Patient safety outcomes can be contributed to the monitoring of ADRs through the execution of pharmacovigilance activities. It is known that spontaneous reporting of ADR is an important tool to gather safety information for the symptoms to be detected earlier. Spontaneous reporting course is a widespread method of drug surveillance and it is capable in recognising ADRs in the daily medical practice although it is known to have several disadvantages such as underreporting and absence of information on the number of people actually exposed to the drug. Reports received by each national pharmacovigilance centre will then be sent to the WHO Collaborating Centre for International Drug Monitoring to be compiled and analysed.

Malaysia's current reporting system of adverse drug reactions involves a passive approach where health care providers, pharmaceutical industries and patients or consumers can lodge their reports online or via prepaid postage report forms. The reports from marketing authorisation holders or pharmaceutical companies are compulsory whereas the reports from healthcare practitioners and consumers are on a voluntary basis. This voluntary basis is also well known as spontaneous reporting system of adverse drug reactions and it is one of the methods to increase the awareness and strengthen the knowledge of the health care key players as well as the consumer on the risks of medicines in clinical practice. This system of ADR reporting is the cheapest and easiest to establish and run. However, there are a few weaknesses following this system i.e. underreporting and bias (Hazell & Shakir, 2006).

In Malaysia, National Centre for Adverse Drug Reaction which is based in NPCB, is a WHO-approved pharmacovigilance centre. It acts as a secretariat to Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and in 1990, it was accepted as the 30th member of the World Health Organisation (WHO) Program for International Drug Monitoring. MADRAC was established under Drug Control Authority (DCA) in order to carry out the function of pharmacovigilance for registered drugs in Malaysia. MADRAC monitors all types of drugs used by human such as vaccines, biologicals and herbal remedies and the records are maintained manually. MADRAC provides important information pertaining to local and international drug safety issues and also provides advice to DCA on risk management and risk communication subsequent to effective assessment of the benefit-risk profile of drugs. Other core functions of MADRAC include promoting ADR reporting in Malaysia, provide reliable information and advices to DCA on drug safety, disseminate drug safety information to healthcare professionals and participate in global pharmacovigilance activities via the WHO Programme for International Drug Monitoring. Under the WHO Program for International Drug Monitoring, MADRAC will receive and assess all adverse drug reactions reports and subsequently forward them to central WHO Global ICSR (individual case safety report) database. This database is maintained by the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre in Sweden. ("About the Malaysian Adverse Drug Reactions Advisory Committee," 2012).

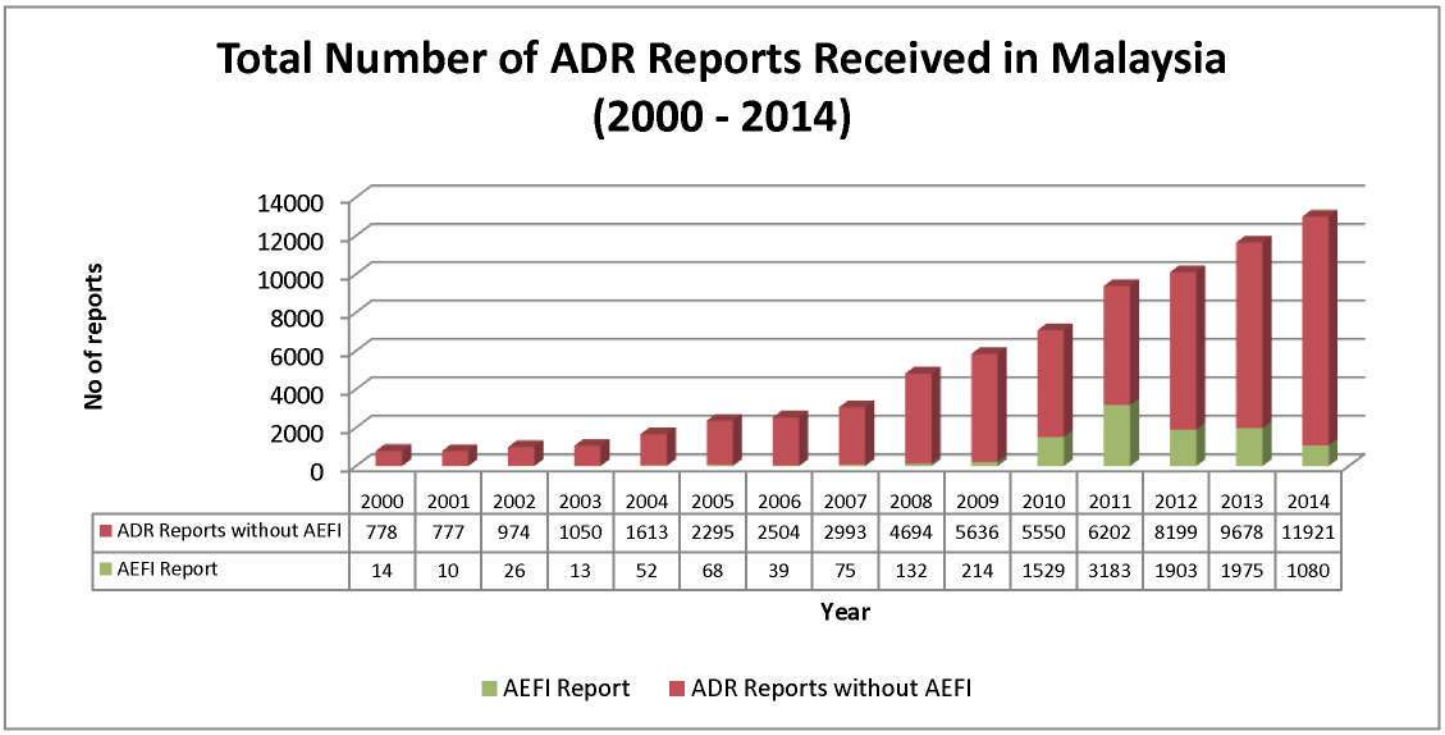


Figure 2.1: Number of ADR reports sent to NPCB from 2000 until 2014

The NPCB strives to ensure the safety of medicinal products registered in Malaysia through monitoring of ADR reports, identification and review of local and international drug safety issues, training and risk communication. Besides the traditional role of assessing ADR reports, NPCB conducted active surveillance to detect ADR signals which may indicate potential drug safety problems, monitored local and international drug safety issues, and implemented risk minimisation strategies. The number of ADR reports received by the NPCB has been steadily increasing since 2000. After being presented and approved at MADRAC meetings, the reports were submitted to be included in the WHO International Database of ADR reports. As seen in Figure 2, there was a 13.4% increase in the total number of ADR reports received in 2014 as compared to the previous year. This shows that the awareness of the importance of ADR reporting has increased and continues to rise.

2.3 Drug-induced renal disorders

In present clinical practice, drug-induced renal disease constitutes as an important cause of acute renal failure and chronic renal disease. Renal injury occurs when kidney-specific detoxification and excretion do not work properly due to the damage or destruction of kidney function by exogenous or endogenous toxicants (Kim & Moon, 2012). Thus, drug-induced renal injury is the damage or destruction of kidney functions caused by the consumption of possible suspected drug or medication. Different classes of drugs or medicines initiate certain stereotyped kidney responses by virtue of immunological mechanisms or direct toxicity. For most patients suffering from drug-induced nephropathy, common risk factors which precipitate the adverse effects of kidney injury include: age, pre-existing renal dysfunction, volume-depleted state and coexisting use of other nephrotoxins. A few prototype drugs are well-recognised although it is impossible to present all the drugs that result in renal disease. A possibility of drug-induced renal failure should be kept as the prompt removal of the drug in a case of undiagnosed renal disease and supportive management can reverse the renal dysfunction to a large extent.

In recent days, the incidence of drug-induced nephrotoxicity has been increasing with the ever increasing number of medicines and with easily obtained over-the-counter (OTC) medicines. Among the drugs reported to be major culprits to kidney damage include antibiotics, NSAIDs, angiotensin converting enzyme inhibitors (ACEI) and contrast agents. In an Indian study by Jha and Chugh (1995), drug-induced renal failure accounted for 20% of all acute renal failure in which most of it caused by aminoglycoside (accounted for around 40% of all acute renal failure cases). The four most common mechanisms of drug-induced nephrotoxicity include (1) vasoconstriction, (2) altered intraglomerular hemodynamics, (3) direct tubular toxicity, and (4) acute interstitial nephritis (Blatt & Liebman, 2013). Examples of symptoms that lead to renal disorders include pre-renal failure / functional renal failure, acute tubular interstitial, acute interstitial nephritis and drug-induced crystalluria (Ganguli & Prakash, 2003)

Su, Hsieh and Gau (2007) conducted a study on drug drug-induced renal disorders based on spontaneous ADR reports. According to their study, they found that the most frequent reported suspected drugs in Taiwan were gentamicin (9.1%), followed by vancomycin (3.9%), warfarin (3.3%), amphotericin B (3.3%) and cyclosporin (2.8%). However, in most of the

literature reports, aminoglycoside antibiotics (AMGs), radiocontrast media, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and diuretics are frequently implicated (Davidman, Olson, & Kohen, 1991). Table 2.1 shows mechanisms of drug-induced kidney injury with some examples.

Table 2.1: Mechanisms of drug-induced kidney injury with some examples

Acute renal failure	
Pre-renal failure	
Impaired glomerular haemofiltration	
ACE inhibitors	Important clinical and laboratory findings:
Angiotensin receptor blockers	Urinary sodium excretion decreased
NSAIDs	Urinary sediment: clear
COX-2 inhibitors	
Diuretics	
Calcineurin inhibitors (cyclosporin, tacrolimus)	
Intrinsic renal causes	
Acute tubular necrosis	
Aminoglycosides	Important clinical and laboratory findings:
Amphotericin B	Sudden rise in creatinine
Cisplatin	Urinary sodium excretion increased
Radiocontrast media	Urinary sediment: granular casts and renal epithelial cells
Tubulointerstitial nephritis	
Antibiotics (penicillins, cephalosporins, sulphonamides, fluoroquinolones, rifampicin)	Important clinical and laboratory findings: Sudden rise in creatinine
NSAIDs	Systemic manifestations of a hypersensitivity reaction: e.g. fever, rash and eosinophilia
Thiazide diuretics	
Lithium	Urinary sediment: white blood cells (often eosinophils) and casts and proteinuria
Proton-pump inhibitors	
Anti-epileptic drugs (phenytoin, valproic acid, carbamazepine)	
Allopurinol	
Thrombotic microangiopathy	
Calcineurin inhibitors (cyclosporin, tacrolimus)	Important clinical and laboratory findings:
Chemotherapeutic drugs (mitomycin C, bleomycin, cisplatin)	Sudden rise in creatinine
Oestrogen-containing oral contraceptives	Fever, haemolytic anaemia, thrombocytopenia, renal impairment and neurological dysfunction
Clopidogrel	
Quinine	
Obstructive causes	
Crystal-induced tubulointerstial disease/ obstructive uropathy	
Acyclovir	Important clinical and laboratory findings:
Indinavir	Urinary sediment: red and white blood cells, granular casts and characteristic drug crystals
Sulphonamides	
Methotrexate	
Ciprofloxacin	
Sodium phosphate	
Chronic renal failure	
Tubulointerstitial nephritis	
Lithium	Important clinical and laboratory findings:
NSAIDs	Gradually declining renal function
Nephrotic syndrome	
Glomerular disease	
NSAIDs	Important clinical and laboratory findings:
Lithium	Marked proteinuria, may be accompanied by haematuria and hypertension
Interferon α and β	
Pamidronate	
Sirolimus	
Tubulopathies	
Fanconi's syndrome	
Tenofovir	Important clinical and laboratory findings: Proteinuria, phosphaturia, glycosuria and bicarbonate wasting

NSAIDs = non-steroidal anti-inflammatory drugs; ACE = angiotensin-converting enzyme; COX = cyclo-oxygenase.

In an article, Bellomo (2006) indicated that drugs caused almost 20% of community and hospital acquired episodes of acute renal failure. As compared to three (3) decades ago, in average, patients nowadays are older, have more comorbidities (higher incidence of diabetes, cardiovascular disease and other chronic conditions), prescribed with multiple medications and are exposed to many diagnostic and therapeutic procedures and agents with the potential to harm kidney function. Some of these agents cause adverse drug effects that are linked to systemic toxicity including nephrotoxicity which results in serious clinical syndromes such as acute kidney injury (Pazhayattil, 2014). Uchino et. al (2005) reported in their study that nephrotoxic agents have been implicated as etiologic factors in 17%–26% of in-hospital acute kidney injury cases. A prospective study by Kohli Bhaskaran and Muthukumar (2000) found that among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66%. The renal impairment can sometimes be reversible once the offending drug is stopped. However, the condition can be more costly, require several interventions and may necessitate hospitalization. Drugs causing renal injuries could exert their toxic effects through one or more pathogenic mechanisms and the injuries tend to be more frequent among patients in specific clinical conditions (Naughton, 2008). Among the pathophysiologic mechanism of renal injury include altered intraglomerular hemodynamics, tubular cell toxicity, crystal nephropathy, inflammation, thrombotic microangiopathy, and rhabdomyolysis (Schetz, Dasta, Goldstein, & Golper, 2005; Zager, 1997). It is important for health care professionals to have the knowledge on the drugs and their particular pathogenic mechanisms of kidney injuries so that it will be easy to recognise, manage and most importantly, to prevent the occurrence of drug-induce renal impairment. Based on the hospitalisation rates, morbidity, and mortality associated with renal impairment, knowledge of the typical agents associated with nephrotoxicity is critical in improving the ADR rates and outcomes (Waikar, Liu, & Chertow, 2008). Drug-induced renal impairment involves many classes of drugs and includes prescription agents as well as commonly encountered over-the-counter drugs.

2.3.1 Classification of drug-induced nephrotoxicity

Our kidneys are exposed to so many drugs. There are drugs with high concentration of drugs and their metabolites – thus, making the precious organs vulnerable to drug toxicity. As stated by Decloedt and Maartens (2011), drug-induced renal impairment contributes up to 25% of all cases of acute kidney injury. The injury caused by offending drugs may cause predictable, cumulative dose-dependent toxicity or idiosyncratic dose-independent toxicity at any time throughout treatment. Cumulative dose-dependent toxicity can be predicted and prevented. However, idiosyncratic dose-independent toxicity cannot be anticipated and avoided. A basic knowledge on drug-induced kidney disorder is really important in managing the toxicity and enables a vigilant approach in prescribing, dispensing and administering drugs that can potentially cause renal toxicity.

Renal impairment may occur in different renal sites or compartments which may include the glomerulus, the renal vascular supply, and the tubulointerstitium where extensive tubular-peritubular caplliary exchange of solutes takes place, as well as collecting ducts. Basically, the drug-induced renal toxicity is classified into four major renal syndromes which are (Decloedt & Maartens, 2011):

1) Acute renal failure
2) Chronic renal failure
3) Glomerulonephritis
4) Tubulopathies

2.3.1.1 Acute renal failure

Classically, acute renal failure (ARF) is defined as an "*abrupt and sustained decrease in renal function*" (Bouman & Kellum, 2010). The clinical condition of acute renal failure (ARF) is said to occur in anywhere from 1% to 25% of critically ill patients (Chertow, Levy, & Hammermeiter, KE, 1998; de Mendonca, Vincent, & Suter, PM, 2000) and it depends on the population being studied plus the criteria used to define its presence. A new classification scheme for acute kidney injury was established by the Acute Dialysis Quality Initiative (ADQI)

group. The group defines grades of increasing severity of acute renal injury into five class i.e. risk (class R), injury (class I) and failure (class F) - plus two outcomes class (loss and end-stage kidney disease). The classification system includes separate criteria for creatinine and urine output. As an example, Hoste et al (2007) used this classification scheme and they found that acute renal impairment occurred in 67% of ICU admissions with maximum R, I, F class of 12%, 27% and 28%, respectively. Figure 4 summarises the ADQI consensus criteria for acute renal failure

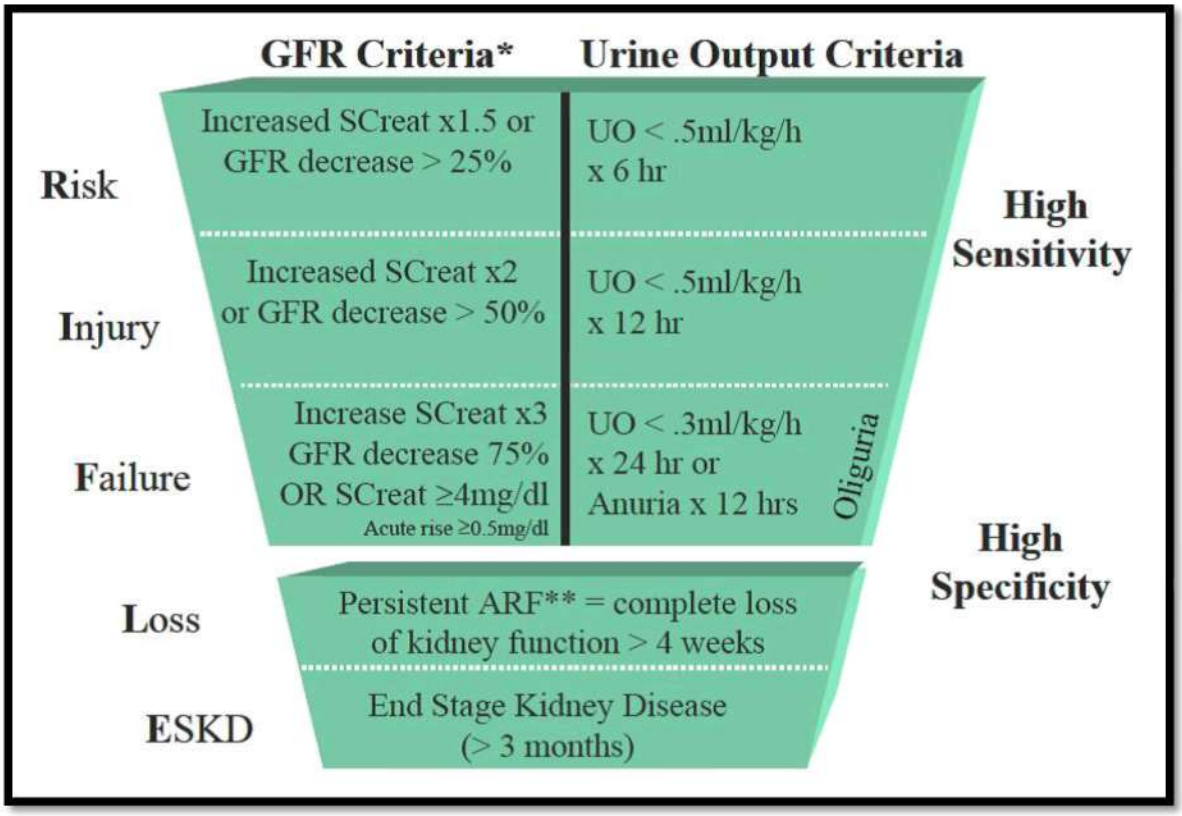


Figure 2.2: Proposed classification scheme for acute renal failure by ADQI

Choudhury (2006) and Schetz et al. (2005) reported that nephrotoxicity due to drugs contributes to between 8-60% of acute renal injury cases in hospitalised patients. Elderly patients are likely more susceptible to acute renal injury from nephrotoxic agents related to the age-related decline in glomerular filtration rate or renal blood leading to reduced clearance of the drug. Generally, drug-induced nephrotoxicity is reversible. However, given the high morbidity and mortality associated with acute renal impairment and the frequent and necessary use of drugs

in critically ill patients, clinicians should be aware of the potential nephrotoxicities and mechanisms (Rosner & Okusa, 2010).

Drugs can induce acute renal injury by causing pre-renal, intrinsic or post-renal toxicity (obstructive nephropathy). Pre-renal toxicity occurs when the drugs impair the glomerular hemofiltration. Drugs can cause reduction of the renal blood perfusion by altering the vasomotor tone of the afferent (pre-glomerular) or efferent (postglomerular) arterioles and decrease the glomerular filtration rate with consequent renal failure. Patients with compromised renal perfusion (e.g. volume depletion or heart failure) are mostly at risk. Intrinsic renal or intrarenal disease is a type of kidney disease that often occurs when direct damage to the kidneys causes a sudden loss in kidney function. The disease also is caused by lack of blood to the kidneys, drug abuse and inflammation from other causes.

Currently, there are still no standard guidelines used to infer changes in serum creatinine. Nevertheless, there a few biochemical criteria which have been used to indicate acute renal failure (Schoolwerth, Sica, Ballermann, & Wilcox, 2001). Those biochemical criteria include:

1) a rise of 50% serum creatinine from baseline, or,
2) an increase of 0.5 mg/dL (40 μmol/L) or more when baseline serum creatinine is less than 2 mg/dL (180 μmol/L), or,
3) an increase of 1 mg/dL (90 μmol/L) or more if baseline creatinine is greater than 2 mg/dL

2.3.1.2 Chronic renal failure

Chronic kidney disease is the gradual loss of kidney function and the final stage of chronic kidney disease is called end-stage renal disease (ESRD). Chronic kidney disease leads to a buildup of fluid and waste products in the body. This condition affects most body systems and functions, including high blood pressure, low blood cell count, reduced vitamin D level and bone health. Chronic kidney failure does not usually cause symptoms until it reaches an advanced stage. It is usually detected at earlier stages by blood and urine tests. There are several main symptoms of advanced kidney disease which include tiredness, swollen ankles, feet or hands (due to water retention), shortness of breath, nausea and blood in the urine.

Slow progressive elevation of creatinine concentration is a presentation of drug-induced chronic renal failure. It also usually presented microscopically as tubulointerstitial nephritis. Tubulointerstitial nephritis is characterised by interstitial fibrosis, tubular atrophy and inflammation. Repeated or prolonged acute tubulointerstitial nephritis can direct to chronic tubulointerstitial disease. There are a few drugs known to be associated with chronic tubulointerstitial nephritis without acute episodes such as lithium and non-steroidal anti-inflammatory drugs (NSAIDs) (Decloedt & Maartens, 2011).

A classification of chronic kidney disorder has been established by The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation. Interestingly, this classification has been accepted and used worldwide. This classification defines chronic renal disease as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 or a GFR ≥60 mL/min/1.73 m^2 together with the presence of kidney damage for more than 3 months. By referring to this definition, the K/DOQI has recommended a classification of chronic renal disease to be further divided into 5 stages as seen in Table 1 below (Hassan, Al-ramahi, Aziz, & Ghazali, 2009).

Table 2.2: Stages of Chronic Kidney Disease

Stage	Description	GFR ml/min/1.73m^2
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild reduction in GFR	60-89
3	Moderate reduction in GFR	30-59
4	Severe reduction in GFR	15-29
5	Kidney failure (end stage renal failure)	< 15 (need dialysis)

2.3.1.3 Glomerulonephritis

Glomerulonephritis is an inflammation, not an infection, of the tiny filters in the kidney (known as the glomeruli) that filter the blood coming to the kidney via the renal arteries. When the glomeruli are inflamed, red blood cells, white blood cells and protein escape into the urine.

However, this is usually detected by the doctor through the testing of the urine and finding traces of blood or protein ("Glomerulonephritis or nephritis," 2004).

Glomerular dysfunction causes nephritic syndrome and it is marked by heavy proteinuria. Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are primarily caused by podocyte dysfunction. Membranous glomerulonephritis (MGN) is characterised by subepithelial immune complex deposits in the glomerular basement membrane. This disorder tends to be present with proteinuria which can occasionally be severe (>2.5g per 24 hours). NSAIDs are the most common drug implicated and this complication can take place between several weeks to years after treatment initiation (Ranskov, 1999). The condition usually resolves after discontinuing drug therapy. However, continued NSAID therapy may lead to chronic renal impairment (Waring, 2006). Among other drugs which can cause MGN are captopril and penicillamine.

2.3.1.4 Tubulopathies

Tubulopathy is an impairment affecting the renal tubules of the nephrons. Renal tubulopathies form a complex group of rare disorders which result in the inability of the tubule to exert its various functions. Most of tubulopathies are hereditary, though some are acquired secondary to another disease or pharmacotherapy. Generally the consequences of tubular impairment are variable and is dependent on the location within the tubule and the existence, or not, of compensatory pathways. The usual clinical symptoms include loss in the urine of minerals, salts, vitamins; internal environment imbalance (Water balance, acid-base balance disorders for example) and delayed or defective growth (rickets, osteomalacia).

2.4 Predisposing factors of drug-induced nephrotoxicity

Older age, female sex are some of the predisposing factors stated in most literatures which are associated with lower total body water and reduced muscle mass. Decreased total body

water increases the concentration of drug in serum. Both factors work in concert to raise serum drug concentration to potentially toxic levels. In addition to these factors, hypoalbuminemia also carries the risk of inducing toxic drug levels by increasing the unbound drug fraction in the serum. Besides that, the risk of nephrotoxicity is increased in patients with acute kidney injury (AKI) or chronic kidney disease (CKD). Thus, patient who is on diuretic therapy or has vomiting or diarrhea that results in true volume depletion is vulnerable to toxic drug effects on the kidney. Similarly, patient with congestive heart failure or hepatic failure with ascites that has effective volume depletion may experience prerenal AKI and become more susceptible to the nephrotoxic effects of certain agents. This is because cirrhotic patients tend to have reduced muscle mass and hypoalbuminemia. Additional variables in older patients include comorbid conditions that predispose to AKI as well as an increased likelihood of polypharmacy with nephrotoxic drugs.

Another group of age that is at particular risk for drug-induced renal impairment is neonates. In neonates, particularly those with premature delivery, drug nephrotoxicity bears a significant burden for AKI as compared to adult patients and is supported by data that suggest that drug-induced renal impairment leads to 16% of AKI cases in newborns. Several factors may explain this, including increased susceptibility of the neonatal immature kidney to nephrotoxic insults as well as the use of multiple nephrotoxic agents in critically ill newborns.

Based on the previous study on the spontaneous reports by Jose and Rao (2006) in India, at least one predisposing factor was present in 79.9% of the reports whilein 90% of these reports, more than one predisposing factors were suspected to be involved. The most common predisposing factors identified that are associated in the reported reactions included polypharmacy and multiple disease state which was noticed in 93.1% and 52.9% of the reports, respectively. They found that among the reports with polypharmacy as a predisposing factor, mild, moderate and major polypharmacy were present in 25.8, 61.6, and 12.6% of the reports, respectively (Jose & Rao, 2006).

CHAPTER 3

METHODOLOGY

3.1 Research Design and Location of the Study

This is a retrospective study where the data was collected at the Pharmacovigilance Section, Centre of Post Registration Product, National Pharmaceutical Control Bureau (NPCB). This study is descriptive in nature and relies on existing data. The data under observation are quantitative in nature. As stated in the "International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use" (2003), a report in which unsolicited or voluntary contact is made between a regulatory agency and a reporter is a spontaneous report. According to the ICH guidelines, there are a few minimum reporting criteria for an ADR to be accepted and they include identifiable reporter, patient, at least one adverse event and one suspected drug or product.

3.2 Sample Size Calculation

For the purpose of this study, a sample size was not calculated as all spontaneous ADR reports from 2010 to 2014 related to the renal disorders were extracted from the Quest 2 database, regardless of the seriousness. Patient demographics, drug treatment and types of renal injuries were identified and recorded.

3.3 Validity of Data Collection

In order to ensure the validity of data collection, ten (10) reports were initially sampled from the Quest 2 database (computerised data) and these data were compared (crosschecked) with the data from the original reports (hardcopy or softcopy form sent by the reporters). Data clarification with the experts or person- in- charge was also done. When there were some conflicts in the data (at least in one sample), another ten (10) reports were sampled. This process continued until all ten (10) sampled reports have no conflicts and in accordance with the original data. Once there was no discrepancy or conflict between those two softcopy and hardcopy data in any of the samples, the report sampling process was then stopped.

3.4 Study Flow Chart

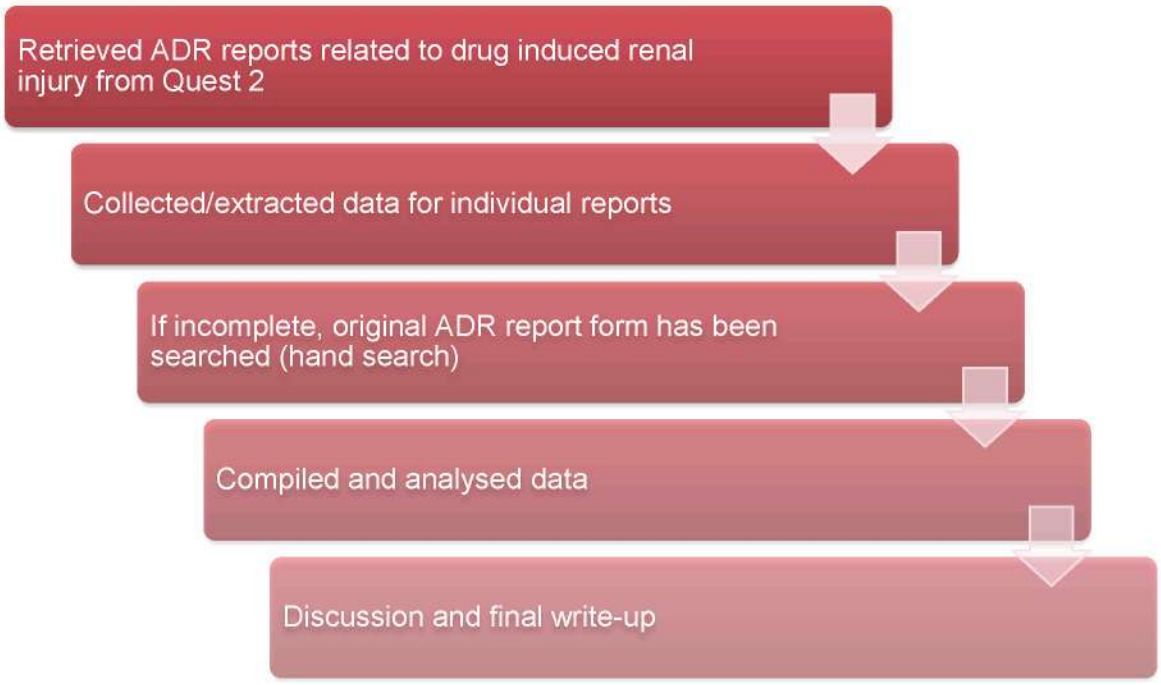


Figure 3.1: Flow chart of the study process

3.5 Ethical Consideration

The approval to commence this study was endorsed by the Research Ethics Committee (REC) of Universiti Teknologi MARA (UiTM) in order to ensure that the research project is conducted in compliance with the national and international conditions and guidelines stipulated in the Good Clinical Practice Guideline, Ministry of Health (MOH), Malaysia and the Declaration of Helsinki, World Medical Association (WMA). An approval from the Research and Ethics Committee (MREC) of the Malaysian Ministry of Health was also obtained as this project will be conducted in the facilities of MOH. Furthermore, this study was registered under National Medical Research Registry (NMRR), approved by the Clinical Research Centre (CRC) Ministry of Health Malaysia and was given with registration ID NMRR-15-203-24512.

A formal letter was given by the pharmacy faculty, UiTM to the Director of Regulatory Pharmacy, NPCB before the study was conducted. All the data that were obtained from the Quest 2 database such as patients' profile and medical records were restricted only for the investigators and were ensured to be kept private and confidential.

3.6 Data Collection

The following information was taken into consideration: (1) source of reports, (2) reporter's designation, (3) patient's age and gender, (4) reporter's diagnosis of the ADR, (5) drug exposure (indication and dosage), (6) concomitant drugs, (7) time of event onset, (8) outcome of the ADR and also (9) the types of renal injury. Reports were classified according to the WHO criteria for causality assessment. By referring to the WHO Adverse Reaction Terminology (2012), the types of renal injury were determined according to system organ class (SOC) of urinary system disorders. Drugs involved in the ADRs were codified into various drug classes according to anatomical therapeutic chemical (ATC) classification based on WHO–ATC Index 2005.

3.6.1 ADR Causality Assessment and Extent of Severity

For each ADR report submitted to MADRAC, the causality assessment is classified into Certain, Probable, Possible, Unlikely and Unclassifiable. The classification is made based on the WHO-Uppsala Monitoring Centre (WHO-UMC) guidelines on causality assessment (WHO-UMC 2005). The extent of severity was recorded based on the severity proclaimed by the reporters and was classified as mild, moderate and severe.

3.6.2 Patient Characteristics

Patients' age, gender, race and number of concomitant drugs received (or polypharmacy) were all considered and evaluated in this study. In agreement with the previous paper by Gallelli et al. (2002), patients will be subdivided into six age groups; infants, children and adolescents (0-15 years), young adults (16–30 years), adults (31–45 years), older adults (46–60 years), elderly adults (61–75 years), and very elderly adults (over 75 years). Based on the description and characterisation by Veehof, Stewart, Haaijer-Ruskamp and Jong, (2000), polypharmacy is considered as minor (0–3 drugs), moderate (4–5 drugs) or major (>5 drugs).

3.6.3 Onset of Time to Renal Injury

As described by Hoigne et al. (1990) the onset of reactions time was distinguished into three categories; acute (from 0 to 60 minutes), sub-acute (from 1 hour to 24 hours) and latent (more than 24 hours).

3.7 Data Selection Criteria

3.7.1 Inclusion criteria

a) All ADR reports related to drug-induced renal injury (classified as 'urinary system disorders' based on System Organ Class (SOC) of the ADR terminology of the WHO) reported to NPCB from 2010 until 2014
b) ADR reports with reactions that were classified as containing Certain, Probable, Possible, Unlikely and Unclassifiable causal relationship with the drug (regardless of the severity) according to the WHO Causality Assessment / Categories.

3.7.2 Exclusion criteria

a) All ADR reports which are non-related to drug-induced renal injuries reported to NPCB.
b) ADR reports which are based on literature reports.
c) ADR reports related to the use or administration of vaccines.
d) ADR reports related to the use or administration of traditional and complementary medicines.

3.8 Data Analysis

3.8.1 Descriptive Statistical Analysis

The data were analysed using Microsoft Excel and Statistical Package for Social Science (SPSS) version 22 software. Descriptive statistical analyses were carried out to describe the demographic data and pattern or trends of the drug induced renal injuries reported in Malaysia. A descriptive analysis was also done on reported drugs that are common in causing renal injury in Malaysia. Mean, standard deviation (SD) and the percentage were determined and presented.

3.8.2 Inferential Statistical Analysis

The null hypotheses mentioned earlier were tested by using Pearson's chi-square test in order to determine the association between the studied variables (e.g. age, gender, race, concomitant drugs) with the extent of severity. A significance level was set at α=0.05. A p-value of <0.05 is considered statistically significant.

Factors which could have predisposed to the occurrence of renal impairment were also evaluated. Predisposing factors that were considered for the purpose of this study include age, gender, race, dosage of the drug, number of concomitant drugs (polypharmacy) and the combination of drugs. Multiple logistic regressions were applied to determine the association between predisposing factors of drug induced renal injuries with the extent of severity. Analyses on the relationship of the intended ADR with the predictors (independent variables) were statistically analysed using simple logistic regression (univariate analysis) and binary logistic regressions (multivariate analysis). All variables that scored a p-value which is less than 0.25 during univariate analysis were included in the multivariate analysis. The backward and forward stepwise logistic regressions were run and used for the variable under interest (extent of severity) which was binary. The final model was checked by using the Hosmer-Lemeshow test. The analyses were presented with adjusted odds ratios with 95% confidence intervals, Wald statistics and p-value where necessary. Again, significance level was set at α=0.05 and a p-value of <0.05 was considered statistically significant.

CHAPTER 4

RESULTS

4.1 Pattern / trend of adverse drug reaction related to drug induced renal injuries spontaneously reported in Malaysia (2010 – 2014).

4.1.1 Pattern / trend of ADR reports in Malaysia according to sources of reports

In the 5-years period from January 2010 until December 2014, a total of 2093 reports which is related to drug-induced renal injuries were extracted from the Quest 2 database. After the removal of possible duplications and exclusion of reports derived from literatures, a finalised number of 1874 reports were considered to be analysed throughout this study. From the report, since more than one drug might be implicated in a report, 2086 drugs were recorded as the suspected drugs that induced renal injuries (1.11 drugs per report).

According to the sources of reports, Selangor was found to be the state with the highest number of reports sent to NPCB (n = 389; 20.8%). This is followed by Kuala Lumpur (n = 207; 11%) and Perak (n = 186; 9.9%). Table 4.1 shows the number of drug-induced renal injuries reported in Malaysia according to states in Malaysia. By institutions (Table 4.2), government hospitals sent the highest number of reports with a number of 1334 reports (71.2%). Private sectors were led by the pharmaceutical companies with a total number of reports of 183 (9.8%). Almost sixty-seven percent of the reports (n = 1249) were sent by pharmacists, followed by medical officers that are working in government hospitals (n = 246, 13.1%). The trend of drug-induced renal injuries report is shown in Table 4.3.

Table 4.1: Trends of ADR related to drug-induced renal injuries reported according to states in Malaysia

State	Data (N = 1874)	
	n	%
WP Labuan	13	0.7
Perlis	15	0.8
Kelantan	57	3.0
Kedah	62	3.3
Terengganu	69	3.7
Pahang	83	4.4
Johor	99	5.3
Sarawak	106	5.7
Melaka	112	6.0
N Sembilan	138	7.4
P Pinang	144	7.7
Sabah	171	9.1
Perak	186	9.9
WP Kuala Lumpur	207	11.0
Selangor	389	20.8
Missing Data	23	1.2

Table 4.2: Number of drug-induced renal injuries reported in Malaysia according to institutions

Institution	N = 1874 n	%
Community pharmacy	1	0.1
Dental clinic	1	0.1
Private clinic	4	0.2
University hospital	35	1.9
Private hospital	37	2.0
Pharmaceutical company	183	9.8
Government clinic	272	14.5
Government hospital	1334	71.2
Missing data	7	0.4

Table 4.3: Number of drug-induced renal injuries reported in Malaysia according to reporter's designation

Designation	(N = 1874) n	%
Dentist	1	0.1
General practitioner (GP)	1	0.1
Medical assistant (MA)	1	0.1
Housemen (HO)	4	0.2
Nurse	5	0.3
Consultant	6	0.3
Specialist	39	2.1
Provisional registered pharmacist (PRP)	56	3.0
Pharmaceutical company	183	9.8
Medical officer (MO)	246	13.1
Pharmacist	1249	66.6
Missing data	83	4.4

4.1.2 Pattern / trend of ADR reports in Malaysia according to patients' demography

According to the patients' demography (as presented in Table 4.4), fifty-two percent (52%) of the patients with the studied ADRs were women and almost half of them (n = 927; 49.5%) were Malay, followed by Chinese with 16.8% (n = 315), Indian with 12.8% (n = 239) and other races with 9.0% (n = 168). Out of 1874 reports, 225 (12.0%) of the ADR reports have missing data in terms of the race of patients. The mean age of patients was 42.97 (SD ± 21.49). Patients within 46 to 60 years old were found to be highest group of patients reported with drug-induced renal injuries (n = 501; 24.1%). Patients who are more than 75 years old were found to be the least reported patient with ADRs related to drug-induced renal injury (n = 76; 4.1%). Chi square tests were conducted to point out the association between patient related risk factors and the extent of severity. The results showed that there is no association between gender ($P = 0.181$), race ($P = 0.269$) and age groups ($P = 0.563$) with the extent of severity (Table 4.5).

Table 4.4: Data of ADR related to drug-induced renal injuries reported in Malaysia according to patients' demography

Data (N = 1874)			
Characteristics	**No. (%) of ADR reports**	**Characteristics**	**No. (%) of ADR reports**
Gender		**Age group**	
Male	847 (45.2)	0 to 15	240 (12.8)
Female	976 (52.1)	16 to 30	291 (15.5)
Not reported	51 (2.7)	31 to 45	452 (24.1)
		46 to 60	501 (26.7)
Race		61 to 75	314 (16.8)
Malay	927 (49.5)	> 75	76 (4.1)
Chinese	315 (16.8)		
Indian	239 (12.8)		
Others	168 (9.0)		
Not reported	225 (12.0)		

Table 4.5: Chi square test of association between risk factors and severity of renal injury

Variables	Extent of Injury [n (%)]			p value
	Mild	Moderate	Severe	
Gender				
- Male	219 (28.2)	421 (54.2)	137 (17.6)	0.181
- Female	290 (32.3)	461 (51.4)	146 (16.3)	
Age (Years)				
- 0-15	61 (26.9)	124 (54.6)	42 (18.5)	0.269
- 16-30	97 (34.3)	142 (50.2)	44 (15.5)	
- 31-45	122 (33.1)	191 (51.8)	56 (15.2)	
- 46-60	132 (28.4)	262 (56.3)	71 (15.3)	
- 61-75	85 (29.4)	144 (49.8)	60 (20.8)	
- >75	19 (33.9)	25 (44.6)	12 (21.4)	
Race				
- Malay	277 (55.6)	488 (57.2)	145 (55.6)	0.563
- Chinese	88 (17.7)	159 (18.6)	56 (21.5)	
- Indian	81 (16.3)	123 (14.4)	30 (11.5)	
- Others	52 (10.4)	83 (9.7)	30 (11.5)	

* Chi-square test, $p<0.05$ as significant at 95% CI

4.1.3 Analysis of ADR reports according to causality and extent of severity

Upon causality assessment, it was found that more than three-quarter of the reports (n = 1606, 85.7%) were classified as possible, followed by probable (10.7%) and certain (3.3%). From the reported reactions, almost half of the cases were reported with a moderate extent of severity (47.4%). Mild reactions accounted for 27.5% while only 15.2% of the reactions were deemed to be severe as presented in Table 4.6.

Table 4.6: Analysis of ADR related to drug-induced renal injuries reported in Malaysia according to reaction's causality and the extent of severity

Parameters	Data (N = 1874) Number (%) of ADR
Causality	
- C1 (Certain)	62 (3.3)
- C2 (Probable)	200 (10.7)
- C3 (Possible)	1606 (85.7)
- C4 (Unlikely)	3 (0.2)
- C5 (Unclassifiable)	3 (0.2)
Extent of severity	
- Mild	516 (27.5)
- Moderate	888 (47.4)
- Severe	285 (15.2)
- Not reported	185 (9.9)

4.1.4 Number of concomitant drugs

As depicted in Table 4.7, among the reports with concomitant drugs, mild, moderate and major use of multiple drugs were present in 90.6%, 6.6% and 281% of the reports respectively. A majority of the reports stated that the use of multiple drugs does not exceed 3 drugs. Chi square test showed that there is a significant association between concomitant drug groups and the extent of severity. The result of the test (as shown in Table 4.8) pointed out that the group of 0 – 3 drugs has a higher occurrence of severe type of reactions (76.1%; $P = < 0.001$).

Table 4.7: Analysis of ADR reports according to number of concomitant drug groups

	Data (N = 1874)	
Number of concomitant drug groups	**n**	**%**
0 - 3 drugs (mild)	1698	90.6
4 - 5 drugs (moderate)	123	6.6
≥ 6 drugs (major)	53	2.8

Table 4.8: Chi square test of association between concomitant drug groups and severity of renal injury

Variable	**Extent of Injury [n (%)]**			**p value**
	Mild	**Moderate**	**Severe**	
Concomitant drug groups				
- 0 - 3 drugs	463 (89.7)	753 (84.8)	217 (76.1)	< 0.001
- 4 - 5 drugs	24 (4.7)	63 (7.1)	29 (10.2)	
- ≥ 6 drugs	29 (5.6)	72 (8.1)	39 (13.7)	

* Chi-square test, $p<0.05$ as significant at 95% CI

4.1.5 Trends of onset of time to renal injury reported in Malaysia

Table 4.9 presents the data of drug-induced renal injuries according to the onset of reaction time. Most of cases were reported with sub-acute reaction (n = 730; 39.0%), followed by latent reactions (n = 475; 25.3%) and acute reactions (n = 275; 14.7%). A chi square test was done to determine the association between onsets of time category and the extent of severity (Table 4.10). The test proved that there is a significant association between onsets of time category and the extent of severity ($P = < 0.001$) where the latent onset of time has a higher occurrence of severe adverse reactions (41.6%).

Table 4.9: Analysis of renal injuries according to the onset of time

Onset of time category	Data (N = 1874)	
	n	%
Acute	275	14.7
Sub-acute	730	39.0
Latent	475	25.3
Not reported	394	21.0

Table 4.10: Chi square analysis of association between onsets of time with the extent of severity

Variable	Extent of Injury [n (%)]			p value
	Mild	Moderate	Severe	
Onset of time category				
- Acute	71 (16.9)	156 (20.5)	44 (18.5)	< 0.001
- Sub-acute	250 (59.5)	367 (48.3)	95 (39.9)	
- Latent	99 (23.6)	237 (31.2)	99 (41.6)	

* Chi-square test, $p<0.05$ as significant at 95% CI

4.1.6 Analysis of ADR reports according to outcome of the ADRs

In a majority (67.1%) of the reports, patients experienced a definite improvement after the dechallenge (omission or decrease in dose) of the suspected drugs. 17.3% of the patients did not improve after dechallenge action. Only 1.9% of the cases where the medications were still continued and no dechallenge were done. After rechallenge, 35 of the 45 cases (1.9%) had recurrence of symptoms. Most of the reports (95.5%) recorded that no rechallenge was performed. In 66.3% of the reports, as the final outcome, the patients recovered without sequele from the reactions at the time of the reporting of the ADR. Out of 1874 ADR reports received, 342 cases (18.2%) have not yet recovered from the ADR at the time of reporting. Death cases were also reported where 10 cases (0.5%) may be contributed by the drug, 3 cases (0.2%) were due to the adverse reactions or renal injuries and 8 cases (0.4%) were reported unrelated to the use of the drugs. Table 4.11 summarises the analysis of ADR related to drug-induced renal injuries reported in Malaysia according to the outcome of related ADRs.

Table 4.11: Analysis of ADR related to drug-induced renal injuries reported in Malaysia according to the outcome of related ADRs

Outcome	Data (N = 1874) Number (%) of ADR
After dechallenge	
Definite improvement	1258 (67.1)
No improvement	324 (17.3)
Medication continued	36 (1.9)
Unknown	256 (13.7)
After rechallenge	
Recurrence of symptoms	35 (1.9)
No recurrence of symptoms	10 (0.5)
No rechallenge performed	1790 (95.5)
Unknown	39 (2.1)
Final outcome	
Recovered without sequele	1243 (66.3)
Recovered with sequele	2 (0.1)
Death – drug may be contributory	10 (0.5)
Death – due to adverse reaction	3 (0.2)
Death – unrelated to drug	8 (0.4)
Not yet recovered	342 (18.2)
Unknown	266 (14.2)

4.1.7 Types of ADR related to drug induced renal injuries reported in Malaysia

Overall, 85 types of renal injuries were reported and recorded along this study. One report may have more than one type of renal injury cases. Out of 1904 cases, face oedema was found to be on the top of the list with more than half (n = 1157, 60.8%) of cases reported. This is followed by creatinine blood increase (n = 173, 9.1%) and haematuria (n = 112, 5.9%) at second and third place respectively. Table 4.12 shows the data of top 20 renal injuries that were reported in Malaysia from 2010 until 2014.

Table 4.12: Data of top 20 types of ADR related to renal injury reported in Malaysia

		(N = 1904)	
No	**Types of renal injury**	**n**	**%**
1.	Face oedema	1157	60.8
2.	Creatinine blood increased	173	9.1
3.	Haematuria	112	5.9
4.	Renal failure acute	66	3.5
5.	Renal impairment	38	2.0
6.	Urinary retention	27	1.4
7.	Urinary frequency	25	1.3
8.	Urine discolouration	23	1.2
9.	Dysuria	22	1.2
10.	Nocturia	19	1.0
11.	Urea blood level increased	19	1.0
12.	Renal function abnormal	17	0.9
13.	Polyuria	13	0.7
14.	Difficulty in micturition	12	0.6
15.	Creatinine clearance decreased	10	0.5
16.	Urinary incontinence	10	0.5
17.	Urine abnormal	10	0.5
18.	Proteinuria	9	0.5
19.	Urinary tract infection	9	0.5
20.	Renal function tests nos abnormal	7	0.4

4.2 Common drugs causing drug induced renal injuries reported in Malaysia (2010 – 2014)

4.2.1 Pharmaceutical groups

Based on the ADR data collected, an analysis of common drugs that causes drug-induced renal injuries was done. It was found that a total of 31 pharmaceutical groups were reported to cause renal injuries in Malaysia. A brief comparison of the top 10 pharmaceutical groups across the years 2010 till 2014 was also done in order to look at the pattern of the reported pharmaceutical groups. As presented in Table 4.13, it can be seen that cardiovascular agents, anti-infectives and analgesics are the three groups that are present in the top three of the lists. In 2010, cardiovascular had been on the top of the list. However, the ranking had dropped to the third place in 2012 and maintained that position until 2014. On the other hand, analgesics which was in the third place in 2010, has become the most reported pharmaceutical group to induce renal injuries in 2014. In total, from 2010 until 2014, it was found that analgesic is the highest number of pharmaceutical group reported to cause renal injuries (n = 496; 23.78). This is followed by anti-infectives (n = 448; 21.48%) and cardiovascular agents (n = 380; 18.22%) at the second and third place respectively. Table 4.14 shows the analysis of drugs that caused renal injuries which is reported in Malaysia according to pharmaceutical groups from 2010 until 2014.

Table 4.13: Comparison of top 10 drugs caused renal injuries across years 2010 till 2014 (according to pharmaceutical groups)

Year	2010		2011		2012		2013		2014	
No	**Pharm. group**	**n**	**Pharm. group**	**n**	**Pharm. group**	**n**	**Pharm. group**	**n**	**Pharm. group**	**n**
1	Cardiovascular	83	Cardiovascular	79	Analgesic	103	Antiinfectives	126	Analgesic	142
2	Antiinfectives	61	Analgesic	76	Antiinfectives	85	Analgesic	122	Antiinfectives	111
3	Analgesic	53	Antiinfectives	65	Cardiovascular	78	Cardiovascular	75	Cardiovascular	65
4	Anticoagulant	21	Others	17	Anti-hyperlipidemic	20	Others	30	Others	27
5	Others	17	Anti-hyperlipidemic	15	Antineoplastic	18	Anti-hyperlipidemic	23	Antidiabetic	17
6	Antineoplastic	15	Anticoagulant	12	Others	16	Antineoplastic	21	Immunosuppresive agent	16
7	Antiepileptic	10	Antidiabetic	6	Anticoagulant	13	Antidiabetic	19	Anti-hyperlipidemic	13
8	Antidiabetic	8	Antiviral	6	Antiviral	11	Anticoagulant	14	Antineoplastic	13
9	Anti-hyperlipidemic	7	Antineoplastic	5	Antidiabetic	9	Immunosuppresive agent	14	Antiviral	13
10	Antituberculosis	6	Hormone	5	Antituberculosis	8	Antiepileptic	10	Antiepileptic	12

Table 4.14: Overall analysis of drugs caused renal injuries reported in Malaysia according to pharmaceutical groups from 2010 until 2014

No	Pharmaceutical group	Data (N = 2085)	
		n	%
1.	Analgesic	496	23.78
2.	Antiinfectives	448	21.48
3.	Cardiovascular	380	18.22
4.	Others	107	5.13
5.	Antihyperlipidemic	78	3.74
6.	Antineoplastic	72	3.45
7.	Anticoagulant	70	3.36
8.	Antidiabetic	59	2.83
9.	Antiepileptic	42	2.01
10.	Immunosuppresive agent	41	1.97
11.	Antituberculosis	37	1.77
12.	Antiviral	36	1.73
13.	Antipsychotic	31	1.49
14.	Antiasthmatic	26	1.25
15.	Antihistamine	20	0.96
16.	Vitamin	18	0.86
17.	Antigout	17	0.81
18.	Antidepressant	15	0.72
19.	Antiulcer	13	0.62
20.	Minerals	13	0.62
21.	Corticosteroid	12	0.58
22.	Hormone	11	0.53
23.	Antispasmodic	9	0.43
24.	Contrast media	9	0.43
25.	Antirheumatic	7	0.34
26.	Anesthetic	6	0.29
27.	Antiemetic	6	0.29
28.	Eye preparations	2	0.10
29.	Antihypertensive	1	0.05
30.	Antivenom	1	0.05
31.	Dermatological	1	0.05

4.2.2 Generic names

The collected data were further analysed for common drugs inducing renal injuries according to the generic names of the drugs. From the descriptive analysis, it was found that a total of 346 types of generic were reported and comparisons of top 10 generics were done from the year 2010 until 2014. In Table 4.15, it can be observed that since 2011 till 2014, diclofenac has always been at the top of the list as compared to other generics. It never fails to come in first place and the number of reports also has increased from year to year. The number of cases and the ranking of ibuprofen as one of the most common drug causing renal injuries also kept increasing from 2010 until 2014.

Table 4.15: Comparison of top 10 drugs caused renal injuries across years 2010 till 2014 (according to generic names)

Year	2010		2011		2012		2013		2014	
No	Generic name	n	Generic name	n	Generic name	n	Generic name	n	Generic name	n
1	Aspirin	20	Diclofenac	21	Diclofenac	36	Diclofenac	35	Diclofenac	43
2	Diclofenac	17	Paracetamol	18	Aspirin	19	Ibuprofen	27	Ibuprofen	29
3	Perindopril	16	Amlodipine	16	Paracetamol	15	Aspirin	24	Paracetamol	20
4	Enoxaparin	10	Ibuprofen	16	Ibuprofen	13	Paracetamol	18	Mefenamic acid	19
5	Ibuprofen	10	Aspirin	15	Amlodipine	11	Amoxycillin	16	Amoxycillin/clavulanate	16
6	Amlodipine	9	Perindopril	11	Perindopril	11	Cloxacillin	14	Cloxacillin	16
7	Paracetamol	9	Amoxycillin	8	Amoxycillin	10	Mefenamic acid	12	Perindopril	16
8	Clopidogrel	6	Cloxacillin	7	Cloxacillin	10	Amlodipine	11	Amlodipine	14
9	Fondaparinux	6	Dabigatran	6	Lovastatin	9	Naproxen	10	Aspirin	14
10	Gentamicin	6	Erythromycin	6	Mefenamic acid	9	Simvastatin	10	Methotrexate	12

Overall, from 2010 until 2014, still, it was found that diclofenac has the highest number of reports that cause renal injuries (n = 152; 7.3%) as compared to other generics. This is followed by ibuprofen (n = 95; 4.6%) in second place and aspirin or acetyl salicylic acid (n = 92; 4.4%) in the third position. Table 4.16 illustrates the analysis of drugs which cause renal injuries that are reported in Malaysia according to generic names from 2010 until 2014.

Table 4.16: Analysis of top 20 drugs caused renal injuries reported in Malaysia according to generic names from 2010 until 2014

No	Generic name	n	%
1.	Diclofenac	152	7.3
2.	Ibuprofen	95	4.6
3.	Aspirin	92	4.4
4.	Paracetamol	80	3.8
5.	Amlodipine	61	2.9
6.	Perindopril	61	2.9
7.	Cloxacillin	52	2.5
8.	Mefenamic acid	47	2.3
9.	Amoxycillin	45	2.2
10.	Amoxycillin/clavulanate	34	1.6
11.	Lovastatin	30	1.4
12.	Methotrexate	28	1.3
13.	Simvastatin	27	1.3
14.	Naproxen	26	1.2
15.	Ceftriaxone	25	1.2
16.	Vancomycin	25	1.2
17.	Cefuroxime	24	1.2
18.	Erythromycin	23	1.1
19.	Etoricoxib	22	1.1
20.	Gentamicin	21	1.0

4.2.3 Analysis of most common drug causing renal injuries (2010 – 2014)

Further analyses were conducted to identify the pattern of ADR reports related to renal injuries and was done on the most common drug inducing renal injury i.e. diclofenac. In this study, the age group of patients' age that uses diclofenac is from 1 to 81 years old. Therefore, the mean age for patients with related ADRs were 38.5 years old (SD ± 17.5) and more than half (57.9%) were women. The group of age which used diclofenac the most is between 16 to 30 years old (32.2%). Most of the patients reported to have renal injuries were Malay (57.2%).

Based on the causality assessments of the reports, it was found that 71.7% of the reports indicated that most of the reactions were classified as possible. In terms of extent of severity, it can be observed that the moderate type of severity is the most reported reaction (as shown in Table 4.18). More than half of the cases were reported as moderate for diclofenac (n = 85; 55.9%).

Table 4.17: Data of ADR related to diclofenac-induced renal injuries reported in Malaysia according to patients' demography

(N = 152)			
Characteristics	**No. (%) of ADR reports**	**Characteristics**	**No. (%) of ADR reports**
Gender		**Age group**	
Male	64 (42.1)	0 to 15	13 (8.6)
Female	88 (57.9)	16 to 30	49 (32.2)
		31 to 45	34 (22.4)
Race		46 to 60	35 (23.0)
Malay	87 (57.2)	61 to 75	20 (13.2)
Chinese	21 (13.8)	> 75	1 (0.7)
Indian	30 (19.7)		
Others	13 (8.6)		
Not reported	1 (0.7)		

Table 4.18: Analysis of ADR related to diclofenac-induced renal injuries reported according to reaction's causality and the extent of severity

Parameters	(N = 152) Number (%) of ADR
Causality	
- C1 (Certain)	14 (9.2)
- C2 (Probable)	29 (19.1)
- C3 (Possible)	109 (71.7)
- C4 (Unlikely)	-
- C5 (Unclassifiable)	-
Extent of severity	
- Mild	46 (30.3)
- Moderate	85 (55.9)
- Severe	19 (12.5)
- Not reported	2 (1.3)

According to the analyses of outcome of the ADRs, it can be noticed that most patients experienced a definite improvement after the dechallenge (omission or decrease in dose) of the suspected drugs. Only a few patients did not improve after the dechallenge with 15.8%. Besides that, it also can be observed that no rechallenge activity was performed in almost all cases reported for diclofenac (96.7%). As the final outcome, about three-quarter of the patients had recovered without sequele from the adverse reactions. Table 4.19 summarises the analysis of ADR related to diclofenac-induced renal injuries reported according to the outcome of related ADRs.

Table 4.19: Analysis of ADR related to diclofenac-induced renal injuries according to the outcome of related ADRs

Outcome	Diclofenac (N = 152) Number (%) of ADR
After dechallenge	
Definite improvement	119 (78.3)
No improvement	24 (15.8)
Unknown	9 (5.9)
After rechallenge	
Recurrence of symptoms	1 (0.7)
No recurrence of symptoms	3 (2.0)
No rechallenge performed	147 (96.7)
Unknown	1 (0.7)
Final outcome	
Recovered without sequele	118 (77.6)
Not yet recovered	25 (16.4)
Unknown	9 (5.9)

Table 4.20 presents the data of diclofenac-induced renal injuries according to the onset of reaction time. Most of cases were reported with sub-acute reaction (48.7%) and followed by acute reactions (30.3%) and latent reactions (5.3%).

Table 4.20: Analysis of renal injuries caused by diclofenac according to the onset of time

Onset of time category	Diclofenac (N = 152) Number (%) of reports
Acute	46 (30.3)
Sub-acute	74 (48.7)
Latent	8 (5.3)
Not reported	24 (15.8)

Chi square test was also done to relate the association between the onsets of time and the extent of severity. However, the result indicates that there is no significant association between the two variables ($P = 0.308$).

Table 4.21: Chi square analysis of association between onsets of time with the extent of severity

Variable	Extent of Injury [n (%)]			p value
	Mild	Moderate	Severe	
Onset of time category				
- Acute	8 (22.2)	28 (37.8)	8 (50.0)	0.308
- Sub-acute	26 (72.2)	41 (55.4)	7(43.8)	
- Latent	2 (5.6)	5 (6.8)	1 (6.3)	

* Chi-square test, $p<0.05$ as significant at 95% CI

Table 4.22 represents the types of renal injuries caused by diclofenac. Diclofenac was reported with 8 types of renal injury and the analysis demonstrates that face oedema was the most reported type of renal injury (n = 144; 93.5%).

Table 4.22: Types of renal injuries caused by diclofenac reported in Malaysia

		(N = 154)	
No	**Types of renal injury**	**n**	**%**
1.	Creatinine blood increased	1	0.6
2.	Dysuria	1	0.6
3.	Haematuria	1	0.6
4.	Nephritis interstitial	1	0.6
5.	Nephropathy nos	1	0.6
6.	Decreased urine flow	1	0.6
7.	Acute renal failure	4	2.6
8.	Face oedema	144	93.5

4.3 Predisposing factors/predictors which susceptible to the diclofenac-induced renal injuries

For the purpose of the analysis, the extent of severity were categorised into two categories (i.e. into non-severe and severe reaction) from the initial three groups in order to obtain more presentable analysis. By adjusting a model of binary logistic regression with the variables which include age, gender, race, dosage (in mg) and number of concomitant drugs, the predisposing factors or predictors which were associated with the extent of severity can be predicted.

From the results, it was found that only one variable which is dosage has a significant association with the increase in the severity of reaction. It shows that a unit increase in dosage

would result in 1.017 higher odds of developing non-severe to severe reactions (95% CI: 1.007, 1.028; $P = 0.002$). The rest of studied factors such as age, gender, concomitant drugs, onset of time and combinations of drugs with diclofenac did not show any significant association with the extent of severity (Table 4.23).

Table 4.23: Factors associated with the extent of severity of diclofenac-induced renal injuries among the studied population

Variables	(N = 136)						
	Slogit[a]			Mlogit[b]			
	OR	95% CI	*P* value	Adjusted OR	95% CI	*Wald Statistics*	*P* value
Age (years)	0.015	0.995,1.036	0.144	-	-	-	-
Gender							
Female[c]	-	-	-	-	-	-	-
Male	-0.175	0.417,1.689	0.623				
Race							
Malay[c]	-	-	0.659				
Chinese	-0.296	0.276,2.004	0.558	-	-	-	-
Indian	0.066	0.432,2.637	0.887				
Others	0.828	0.469,11.165	0.306				
Dosage (mg)	0.017	1.007,1.028	0.002	1.017	1.007,1.028	9.971	0.002
Concomitant drug	0.326	0.938,2.049	0.102	-	-	-	-
Drug combination							
Diclofenac alone[c]	-	-	0.234	-	-	-	-
Diclofenac+other analgesics	-0.432	0.210,2.008	0.453				
Diclofenac+antiHPT	0.379	0.281,7.588	0.652				
Diclofenac+others	1.919	0.863,53.823	0.069				

[a] Simple Logistic Regression. Variables with *p* value less than are 0.25 considered into the multivariable selection (Age & Dosage); [b] Multiple Logistic Regression; [c] as reference; Backward LR is used in the multivariable selection; Multicollinearity and interaction not done as the factor (variable) selected is only one

CHAPTER 5

DISCUSSION

5.1 Roles of Spontaneous ADR Reporting

Adverse drug reactions (ADRs) can lead to damaging effects on patients' well-being and to the overall health care system. A wide-range constant ADR programs in the health care system can help to supplement the risk management activities of an organisation, assess the safety of drug therapies, measure related ADR incidences, educate and increase the awareness level of the health care professionals regarding ADRs. Dissemination of this information to the health care professionals assists in promoting drug safety in organizations. Thus, periodic evaluation of ADR data for incidence and pattern is highly essential.

Spontaneous adverse drug reactions monitoring and reporting programs are aimed to facilitate the identification and quantification of the risks associated with the use of drugs. This kind of retrospective study shows that spontaneous adverse reaction reporting can act as a beneficial tool in pharmacovigilance studies. It is notable that drugs safety profiles at the time of regulatory approval are often deficient due to the short duration of studies, limited sample sizes, limited comparison groups, narrowly defined population, narrow set of indications and lack of generalisability of pre-approval clinical trials (Stergachis, Hazlet, & Boudreau, 2008). The pre-marketing conditions under which patients are studied do not fully reflect the way the product will be used in practice once the drug is marketed. Certain adverse effects may not be detected no matter how extensive the pre-clinical work in animals and the clinical trials in patients were carried out until a very large number of people use the product. Thus, post-marketing surveillance is highly needed to detect and evaluate adverse drug reactions (ADRs) of drugs (Ahmad, 2003). Undeniably, information obtained from pharmacovigilance activity is useful to aid in the decision-making process. Moreover, when adequate reporting rates and consumption data are available, it is possible to utilise the spontaneous reporting data to give a useful impression of the frequency of ADRs. The information could lead to changes such as restrictions in product's use, reinforcements of specific warnings and modification in dosage instructions. At

times, a drug may have to be withdrawn from the market when the risk is considered intolerable ("Malaysian Guidelines for the Reporting & Monitoring," 2002)

5.2 Drug-induced renal injuries in Malaysia

Given the kidneys' roles in plasma filtration and maintenance of metabolic homeostasis, toxic effects on the kidney related to medications are both common and expected. Renal toxicity can be a result of direct injury to cells and tissue, inflammatory tissue injury, hemodynamic changes, and/or obstruction of renal excretion. Detection is often delayed until an obvious change in renal functional capacity is measured as there is an increase in serum blood urea nitrogen or creatinine or other physical changes. The true incidence of drug-induced renal injury is therefore difficult to determine. Most episodes of drug-induced renal failure are reversible, with function returning to baseline when the suspected medication is discontinued. Drugs can damage the kidney through dose-related toxic effects on tubular epithelial cells or on the renal vasculature (leading to vasoconstriction and ischemia), or through non-dose-related immunologic mechanisms (Perneger, Whelton, & Klag, 1994)

This study was conducted based on the spontaneous ADR reports sent to National Pharmaceutical Control Bureau (NPCB), reported between January 2010 and December 2014 in Malaysia. An evaluation of the 5-year data was done for various parameters which included sources of reports, patient demographics, drugs and reaction characteristics. Analyses were also done for causality, extent of severity, outcome of the reactions and the predisposing factors related to drug-induced renal injuries caused by most common drug reported in Malaysia.

Overall, a total of 2093 ADRs related to drug-induced renal injuries were reported to NPCB during the 5-year period under consideration. From the extracted data, after removal of possible duplications and exclusion of reports derived from literatures, a number of 1874 reports were considered to be analysed throughout this study. Since more than one drug might be implicated in a report, 2086 drugs were recorded as the suspected drugs that induced renal injuries (1.11 drugs per report). From the descriptive analysis, it was found that Selangor is the

state that sent the highest number of reports to NPCB (n = 389; 20.8%) and this is followed by Kuala Lumpur (n = 207; 11%) and Perak (n = 186; 9.9%). Wilayah Persekutuan Labuan was found to be the state with the lowest number of reports sent to NPCB (n = 13; 0.7%). By institutions, government hospitals sent the highest number of reports with a number of 1334 reports (71.2%). NPCB received ADR reports not only from the government sector, but also from the private sectors. The number of reports by private sectors was led by the pharmaceutical companies with a total number of reports of 183 (9.8%). Almost sixty-seven percent of the reports (n = 1249) were sent by pharmacists, followed by the medical officers working in the government hospitals (n = 246, 13.1%). Pharmacists were found to be the highest number of reporters as the Pharmaceutical Services Division of Ministry of Health Malaysia has set a key performance indicator (KPI) for the pharmacists (in clinical settings) to send ADR reports at least one report per month. Besides that, it is most probably due to pharmacists' role in drug administration and close contact with both physicians and patients.

Analysis on patients' demographics shows that female has a higher number of renal related ADRs (52.1%) as compared to male. Almost half of the cases reported that the patients were Malay (n = 927; 49.5%), followed by Chinese with 16.8% (n = 315), Indian with 12.8% (n = 239) and other races with 9.0% (n = 168). The mean age of patients was 42.97 (SD ± 21.49). Patients within 46 to 60 years old were found to be highest group of patients reported with drug-induced renal injuries (n = 501; 24.1%). Patients who are more than 75 years old were found to be the least reported patients with ADRs related to drug-induced renal injury (n = 76; 4.1%). In India, a prospective cross sectional study by Chatterjee et al. (2015) reported that, the mean age of the patients with drug related renal complications was 45.3 ±16.1 years. However, it needs to be pointed out that the majority of the patients present in the study were males (65.8%).

Concluding causality assessment of the reports was made based on World Health Organization (WHO) causality assessment criteria. Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) committee has made a consensus during their monthly meeting on the final causality of each report. Based on the causality assessment analysis, most of the reactions belonged to the possible category. This pattern followed by probable (10.7%) and certain (3.3%) cases in second and third place respectively. This pattern also similar to the results in another study conducted by Su et al. (2007) in Taiwan.

Considering the extent of the severity of reactions, almost half of the reactions were moderate in severity which is similar to the observations made by other comparable studies (Gholami & Shalviri, 1999; Su et al., 2007). The ranking of severity followed by mild reactions which accounted for 27.5% and only 15.2% of the reactions were deemed to be severe.

Among the reports with concomitant drugs or polypharmacy; mild, moderate and major uses of multiple drugs were present in 90.6%, 6.6% and 281% of the reports respectively. Most of the reports stated that the use of multiple drugs does not exceed 3 drugs.

Many studies have shown that age, gender and number of concomitant drugs are significant risk factors for the development of ADRs (Bates et al., 1999; Evans, Lloyd, Stoddard, Neberker, & Samore, 2005; Gonzalez-Martin, Caroca, & Paris, 1998). In this study, chi-square tests were done to point out the association between patient related risk factors and the extent of severity. However, the results showed that there is no association between gender ($P = 0.181$), race ($P = 0.269$) and age groups ($P = 0.563$) with the extent of severity. The results are different from findings in other studies. A study by Jose and Rao (2006) had concluded that gender was specifically a predisposing factor only in a few (1.5%) of the adverse reaction reports while age (32.4%) was a contributing factor in many of the reports, in which, geriatric group (68.2%) being the major one. Furthermore, a chi-square test was also done to investigate the risk factor of number of concomitant drugs. The result showed that there is a strong association between concomitant drug groups and the extent of severity. The result of the test pointed out that the drug group of 0 – 3 drugs has a higher occurrence of severe type of reactions (76.1%; $P = < 0.001$). Jose and Rao (2006) also revealed that number of drugs is one of the most prevalent predisposing factors in patients who developed ADRs. From their observations, many reports were submitted from the medicine department where usually the patients have multiple co-morbidities. Hence, polypharmacy contributed to the high percentage of reports with these factors as the predisposing ones in their study.

The onsets of time to reactions were counted from the time of the first ingestion of the drugs until the appearance of the adverse reaction. The onset of event was categorised into three groups i.e. acute (less than 60 minutes), sub-acute (1 to 24 hours) and latent (more than 24 hours). Most of cases were reported with sub-acute reaction (n = 730; 39.0%), followed by latent

reactions (n = 475; 25.3%) and acute reactions (n = 275; 14.7%). A chi square test was done to determine the association between onsets of time category and the extent of severity. The test proved that there is a strong association between onsets of time category and the extent of severity ($P = < 0.001$) where the latent onset of time has a higher occurrence of severe adverse reactions (41.6%).

Frequently, drug withdrawal or dose reduction is the first step to be employed for the management of an ADR. In this study, in 84.4% of the reports, the suspected drug was withdrawn or the dose was reduced after the ADR was suspected. Out of that percentage, 67.1% of the patients experienced definite improvements while the rest had no improvement after dechallenge. No change in therapy or additional treatment (medication still continued at the time of reporting) was instituted in 1.9% of cases. Drug rechallenge was done only in 2.4% of reports. Presence of a safer alternative drug and many of the reactions being of the hypersensitivity nature where rechallenge is not a wise option may result in this low number. In majority of the reactions (66.3%), patient recovered completely without sequele, a finding which is similar to the findings on hospitalised patients observed by Suh et al. in their study (Suh, Woodall, Shin, & Hermes-De-Santis, 2000). From this study, it was also found that 13 death cases were reported in which may be caused by drugs or the adverse reactions.

Overall, there were 85 types of renal injuries reported and recorded throughout this study. One report may have more than one type of renal injury cases. Out of 1904 cases, face oedema was found to be at the top of the list with more than half (n = 1157, 60.8%) of the cases reported. This is followed by creatinine blood increase (n = 173, 9.1%) and haematuria (n = 112, 5.9%) in second and third place respectively. Based on a study conducted in Taiwan, Su et al. (2007) list some of the most frequently reported adverse drug reactions which are acute renal failure (26.2%), followed by renal impairment (10.8%), renal failure (9.9%), dysuria (8.7%) and haematuria (8.1%).

An analysis of common drugs causing drug-induced renal injuries reported in Malaysia was performed. It was found that it involved a total of 31 pharmaceutical groups or drug classes. From the comparison of the top 10 pharmaceutical groups from 2010 till 2014, it shows that that cardiovascular agents, analgesics and anti-infectives are the three groups that are always the top

three of the list. In total, from 2010 until 2014, it was found that analgesic is the highest drug class most commonly involved in the reactions of renal injuries (n = 496; 23.78%). This is followed by anti-infectives (n = 448; 21.48%) and cardiovascular agents (n = 380; 18.22%) in second and third place respectively. This finding is consistent with other studies in which analgesics or anti-infectives were most commonly associated with renal injuries (Dasta, Goldstein, Golper, & Schetz, 2010; Davidman et al., 1991).

The collected data were further analysed for common drugs inducing renal injuries according to the generic names of the drugs. From the descriptive analysis, it was found that a total of 346 types of generics were reported and comparisons of top 10 generics were done from 2010 until 2014. As indicated by the results, it can be observed that since 2011 till 2014, diclofenac has never failed to be at the top of the list as compared to the other generics as the number of the diclofenac-induced renal injuries has increased from year by year. Other drugs that were found to be on the top 3 ranking include ibuprofen, aspirin and paracetamol. The number of cases and the ranking of ibuprofen as one of the most common drugs that causes renal injuries also kept increasing from 2010 until 2014. Overall, from 2010 until 2014, still, it was found that diclofenac has the highest number of reports to cause renal injuries (n = 152; 7.3%) as compared to other generics. This is followed by ibuprofen (n = 95; 4.6%) in second place and aspirin or acetyl salicylic acid (n = 92; 4.4%) in third position. As in Malaysia, a report from New Zealand PHARMAC data (renal adverse reaction reports from 1st January 2000 to 31st December 2012) also documented that diclofenac was the most commonly implicated NSAID causing renal adverse effects in the country. As reported by Gallelli et al. (2007), diclofenac is the NSAIDs most frequently involved in the development of ADRs. A study in Italy that assessed the ADR cases based on their spontaneous ADR reporting also mentioned that several cases of acute renal failure in patients with risk factors for renal disorders were also reported for diclofenac (Conforti, Leone, Moretti, Mozzo, & Velo, 2001).

5.3 Analysis of the most reported drug inducing renal injuries and the predisposing factors.

As the most common drug reported to induce renal impairment, diclofenac was further analysed for its pattern of adverse reactions reporting. Globally, the incidence of nephrotoxicity with diclofenac is around 3% (Rehan, Arora, Kumar, & Bhajoni, 2014). Diclofenac (2-[(2,6-dichlorophenyl)amino]phenylacetate) is one of the most frequently used nonselective non-steroidal anti-inflammatory drugs (NSAIDs) and is prescribed to millions of people worldwide for the treatment of osteoarthritis, rheumatoid arthritis, and muscle pain (Hickey, Raje, Reid, Gross, & Ray, 2001; Ng, Vincent, Halliwell, & Wong, 2006).

A precise statistical description of the incidence of renal injuries induced by diclofenac is quite difficult to achieve. This is in view of the heterogeneity of the populations who consume these agents. However, in most general populations, approximately 1-3% of persons exposed to diclofenac will manifest one of several renal injuries that usually require intervention. Although this percentage is relatively low, the numbers of individuals who are "*at risk*" are very high because of the current use of diclofenac profile and its vast availability either by prescription or as an over-the-counter drug. In general, the primary diclofenac related to abnormalities of renal function include (i) fluid and electrolyte disturbances; (ii) acute deterioration of renal function; (iii) nephrotic syndrome with interstitial nephritis and (iv) papillary necrosis (Whelton & Watson, 1991).

Diclofenac exhibits properties of antirheumatic, antiinflammatory, analgesic and antipyretic. It owes its effects to the inhibition of prostaglandins from arachidonic acid by the enzyme cyclooxygenase (COX). Prostaglandins are omnipresent substances that influence a variety of body systems including renal function. They are local hormones that act in a paracrine or autocrine fashion. Prostaglandins are derived from phospholipids and synthesized on demand, not stored in tissues. Oxygenation of arachidonic acid is catalysed by COX and this is the step where NSAIDs carry out the inhibition. Nonselective NSAIDs, like diclofenac, inhibit both COX-1 (constitutively expressed in the kidney) and COX-2 (produced in most tissues in response to inflammation or injury, but also present in normal adult mammalian kidneys), the rate limiting enzymes for the production of prostaglandins. COX-1 functions mainly in the control of renal hemodynamics and glomerular filtration rate (GFR), while COX-2 functions

primarily affect salt and water excretion (Weir, 2002). Different effects on kidney functions may occur if either or both of these enzymes are impeded (Hörl, 2010).

In this study, the reported age of patients' that consume diclofenac was from 1 to 81 years old. The mean age for patients with renal injuries were 38.5 years old (SD ± 17.5) and the group of age which used diclofenac the most was between 16 to 30 years old (32.2%). More than half (57.9%) of the patient reported to have renal injuries were women and most of the patients in this study were Malay (57.2%). A study by Whelton, Lefkowith, West and Verburg (2006) also found that most patients that used diclofenac were females but their average age of the patients was 60 years old. The greater consumption of medications by women may at least partially account for the excess of reports in the female population.

Based on the causality assessments of the reports, it was found that most of the reactions were classified as possible with 71.7%, of the reports. More than half of the cases were reported as moderate for diclofenac (n = 85; 55.9%). According to Whelton and Watson (1991), NSAID-induced renal impairment is basically of moderate severity. This form of drug-induced renal failure is usually reversible over 2-7 days upon discontinuation of therapy (Whelton & Watson, 1991).

According to the analyses of outcome of the ADRs, it can be onserved that most patients experienced a definite improvement after the dechallenge (omission or decrease in dose) of the suspected drugs. Most of the literature have documented that the withdrawal of NSAIDs treatment (including diclofenac) should usually be sufficient to improve renal function (Ashley, n.d.; Dhavinjay, Misra, & Varma, 2013; Whelton & Watson, 1991). In a study by Schneider, Lévesque, Zhang, Hutchinson and Brophy (2006), they concluded that after at least 30 days without a NSAID treatment, the risk of renal failure returned to baseline. In this study, only a few patients did not get any improvement after the dechallenge where 15.8% cases had no improvement. Besides that, it also can be observed that no rechallenge activity was performed in almost all cases reported for diclofenac (96.7%). In the final outcome, about three-quarter of the patients had recovered without sequele from the adverse reactions.

According to the onset of reaction time, most of cases were reported with sub-acute reaction (48.7%), followed by acute reactions (30.3%) and latent reactions (5.3%). This means

that, most of the cases reported happened between 1 to 24 hours after the ingestion of the suspected drug. A study carried out by Krause, Cleper, Eisenstein, and Davidovits (2005) indicated differently. They observed that the time interval between NSAID administration (including diclofenac) and the appearance of the symptoms ranged from 1 to 4 days in their study population (Krause et al., 2005). This means that the appearances of renal injuries observed by them are of latent type of reactions. A chi square test was also done to relate the association between the onsets of time and the extent of severity. However, the result shows no significant association between the two variables ($P = 0.308$).

Furthermore, from this study, diclofenac was also reported with 8 types of urinary system disorders and the results also demonstrate that face oedema was the most reported type (93.5%). This is followed by acute renal failure (2.6%) and decreased urine flow (0.6%). In a study by Whereas Su et al. (2007) reported that the highest reported adverse drug reactions observed from their study were acute renal failure (26.2%), followed by renal impairment (10.8%), renal failure (9.9%), dysuria (8.7%) and haematuria (8.1%). A previous study was conducted to compare the safety profile of celecoxib and nonselective NSAIDs, named CLASS-study, found that oedema, hypertension, and increased creatinine levels occurred more often in diclofenac than in the celecoxib group (Schneider, 2005)

As stated in WHO Adverse Reaction Terminology (2012), according to the system organ class (SOC), face oedema has been listed under urinary system disorders with a code of SOC2 1810 and it is often referred as a symptom of nephrotic syndromes ("Nephrotic Syndrome in Adults," 2012). Edema occurs in approximately 3% to 5% of patients receiving traditional NSAIDs. Sodium chloride and water retention are among the most commonly encountered side effects of the use of NSAIDs. As described briefly by Whelton (1999), NSAIDs can interfere with prostaglandins-mediated mechanisms, decrease sodium transport causing increased sodium chloride absorption. In addition, NSAIDs can interfere with the prostaglandin-mediated antagonism of antidiuretic hormone release. These two physiological events can directly contribute to sodium and water retention, edema, and diuretic resistance (Whelton, 1999). Since it represents a modification of a physiologic control mechanism without the production of a true kidney functional disorder, this may not be considered as a "toxicity" of the drug. In many adults, the formation of detectable edema, related to NSAID use in the absence of obvious renal

functional impairment, is typically seen in less than 5% of such individuals. NSAIDs induced fluid and the electrolyte retention is typically benign, rapidly responds to discontinuation of the drug, and is easily managed in those who require continuous NSAID therapy (Whelton & Watson, 1991).

For the purpose of analyses of this study, from three original categories, the extents of severity were collapsed into two categories (i.e. into non-severe and severe reaction). By adjusting a model of binary logistic regression with the variables age, gender, race, dosage (in mg), number of concomitant drugs and the combination of drug class with diclofenac, the predisposing factors or predictors which were associated with the extent of severity can be predicted. From the result of binary logistic regression, it was found that only one variable which is dosage that has a significant association with the increase in the severity of reactions. The result shows that the increase in a unit of dosage would result in a 1.017 higher odds of developing non-severe to severe reactions (95% CI: 1.007, 1.028; $P = 0.002$). Day and Graham (2013) also discovered that the quantity of administered dose decides the severity of renal complications. In a review, Nderitu et al. (2013) reported that renal failure progression may result from the use of high dose NSAIDs including diclofenac. Contrarily, the rest of the studied factors such as age, gender, concomitant drugs and drugs combination with diclofenac did not show any significant association with the extent of severity.

Although age and number of concomitant drugs (polypharmacy) do not seem to be significant predictors in this study, many studies have related these two variables with the extent of severity of renal injury. In one case-controlled study, the researchers found that not only the risk of renal injury increases with higher diclofenac dose, but also at age that is greater than 65 years, and concomitant use of other nephrotoxic drugs (Gutthann, Rodriguez, Raiford, & et al, 1996). Dhavinjay, Misra and Varma (2013) stated that elderly patients are at an increased risk of contracting renal complications with the use of diclofenac as renal dysfunctions are more prominent in geriatric population with falling renal functions. Whelton and Watson (1991) estimated that, in the absence of other disease entities, the age of 80 years or greater is an independent risk factor since the physiology of aging within the kidney will results in a 50% loss of glomerular function. Blatt and Liebman (2013) reported that nephrotoxicity has a possible

dependence on peak drug concentrations; duration of usage; frequency of dosing; route, rate, and timing of administration; or concomitant use of other nephrotoxins.

The concomitant use or use of diclofenac combined with other drugs is another predisposing factor that is commonly discussed in much literature. Nevertheless, it is found that there is no significant association with the extent of severity in this study. The most commonly reviewed is the combination of diclofenac with antihypertensive drugs. An increase in blood pressure in hypertensive patients may occur due to an interaction between NSAIDs and antihypertensive drugs. This has been documented for the beta blocker agents, the calcium antagonist drugs, the ACE inhibitors (ACEIs), the angiotensin receptor blockers (ARBs) and diuretics. Therefore, from a clinical viewpoint, one can expect that an otherwise stable patient on a given antihypertensive regimen may experience some increase in blood pressure as a result of the addition of an NSAID to their management. NSAIDs may further increase blood pressure, cause fluid retention, and worsen kidney functions. In general, it is not difficult to manage this drug-drug-disease interaction. It must be noted that these patients may require appropriate dosing modification in their antihypertensive regimen (Ganguli & Prakash, 2003b; Whelton & Watson, 1991). In one cross-sectional study of 301 patients, the researchers found that, in comparison with non-use, the use of two or more drugs between diuretics, ACEIs, and angiotensin receptor blockers (ARBs) with NSAIDs was associated with an increased risk of renal impairment (Lapi, Azoulay, Yin, Nessim, & Suissa, 2013). Combinations of ACEIs or ARBs, diuretics and NSAIDs may impair renal function, especially among the elderly (Thomas, 2000). In this study, there are 5 cases of combinations of diclofenac with ACEIs which resulted in 1 mild case, 3 moderate cases and 1 severe case. These cases involve patients from 44 to 81 years old. It can be concluded that age affects the extent of severity as their renal functions deteriorate. Nonetheless, all the patients showed improvement after diclofenac was omitted. There is also a case where a 54 years old patient developed severe renal injury when his antihypertensive regimen (hydrochlorothiazide) was added with diclofenac. It is known that COX inhibition by diclofenac reduces the hydrochlorothiazide-induced urinary sodium excretion significantly and may impair the renal function (Knauf, Bailey, Hasenfuss, & Mutschler, 2006). However, the duration of usage of the combination was not recorded. Fortunately, the complication was reversible as the therapy with diclofenac was discontinued. The patient experienced a definite improvement after diclofenac was withdrawn. In 1992, Seelig et al had

performed a record search of 2278 patients with NSAIDs, 328 with ACEIs, and 162 with both. They claimed that no nephrotoxicity was found in conjunction with monotherapy but three cases of reversible ARF were observed in conjunction with the combination of NSAIDs and ACEIs. Therefore, detailed care is necessary to balance the demonstrated advantages of these medications against the risk of inducing kidney failure.

CHAPTER 6

CONCLUSION, LIMITATIONS & FUTURE RECOMMENDATIONS

6.1 Limitations of the Study

Signal generation and identification of new ADRs are some the strengths of spontaneous reporting system. To date, some studies that compare the safety of different drugs based on spontaneous ADR reporting data have been published. Spontaneous reporting is generally considered as a source of signals and its success depends on the reporting rate and on the quality of reports (Conforti et al., 2001). However, this study has several limitations. The first limitation is underreporting. It is a well-known limitation of spontaneous reporting program that needs to be taken into consideration when interpreting the data. Furthermore, potential confounding factors and bias in reporting should be addressed and the spontaneous reporting data have to be validated by other suitable studies. In some reports, the involvement of a drug is doubtful and further evidence is needed in order to confirm the causality relationship between drug and the adverse reactions. The dissimilarities of certain results in this study can be contributed to the different settings of the studies and the number of samples which is considerably low for the specific drug, i.e. diclofenac. Since the study data was obtained from our national database, the conclusive results can be generalised to the entire population. The data from this study also acts as the preliminary study and provides an insight (especially to the healthcare professionals) on the pattern of ADRs related to renal injuries, which do occur and reported in Malaysia with a comparable pattern of patients' demographics.

6.2 Recommendations and Conclusions

In conclusion, this study has shown the pattern of drug-induced renal failure and urinary system disorders reported in Malaysia. Furthermore, this study has also pointed out diclofenac as the most common drug that causes renal injury aside from demonstrating the trend of renal injuries due to the use of diclofenac. Although diclofenac can be considered as safe and effective

therapeutic NSAIDs for the management of a variety acute and chronic conditions, it has to be used with justifiable cautions. The risk of inducing degeneration of renal function after the initiation of diclofenac is low. However, the number of at-risk patients is high because of the extensive use of it. Similarly, the risk of activating other renal syndromes, for instance the nephrotic syndrome, is uncommon. But, in view of the massive number of individuals who consume diclofenac, the development of this related syndrome must constantly be monitored. Based on the obtained results and comparison with related literature, some preventive measures can be employed. Related predisposing factors have been identified and discussed. It is prudent to avoid high-dose of diclofenac and it should be used with caution especially in elderly patients and in patients that are consuming other drugs at the time especially antihypertensive agents. As advised by The American Geriatric Society (AGS), the use of NSAIDs should be avoided in patients with abnormal renal function. Furthermore, patients who are at-risk of developing renal impairment should not use more than one NSAID at a time (Rose, 1998). Healthcare professionals should have a high awareness of the risks for diclofenac associated renal injuries and need to screen patients appropriately for impairment risk factors before starting diclofenac therapy.

In order to obtained more significant and conclusive results, further study with prolonged period of time is encouraged to be conducted as more cases (samples) can be attained thus providing a more holistic analysis. . Besides that, a prospective study with the focus in capturing the patients' lab results would present a more reliable, credible and accurate in explaining the association of the renal injuries and the extent of severity.

REFERENCES

Aagaard, L., & Hansen, E. H. (2009). Information about ADRs explored by pharmacovigilance approaches: a qualitative review of studies on antibiotics, SSRIs and NSAIDs. *BMC Clin Pharmacol*, *9*.

Aagaard, L., Soendergaard, B., Andersen, E., Kampmann, J. P., & Hansen, E. H. (2007). Creating knowledge about adverse drug reactions: a critical analysis of the Danish reporting system from 1968 to 2005. *Social Science & Medicine (1982)*, *65*(6), 1296–309. doi:10.1016/j.socscimed.2007.04.026

About the Malaysian Adverse Drug Reactions Advisory Committee. (2012).

Ahmad, S. R. (2003). Adverse Drug Event Monitoring at the Food and Drug Administration. *Jounal of Internal General Medicine*, *18*, 57–61.

Aronson, J. K., & Ferner, R. E. (2003). Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ (Clinical Research Ed.)*, *327*(7425), 1222–5. doi:10.1136/bmj.327.7425.1222

Ashley, C. (n.d.). Acute renal failure (p. 26).

ASHP Guidelines on Adverse Drug Reaction Monitoring and Reporting. (1995). *American Journal of Health-System Pharmacy*, *52*, 211–213.

Bates, D., Miller, E., Cullen, D., Burdick, L., Williams, L., & Laird, N. (1999). Patient risk factors for adverse drug events in hospitalized patients. *Arch Intern Med*, *159*.

Bellomo, R. (2006). The epidemiology of acute renal failure: 1975 versus 2005. *Curr Opin Crit Care.*, *12*(6), 557–560.

Bisson, G., Gross, R., Miller, V., & Weller, I. (2003). Monitoring of long-term toxicities of HIV treatments: an international perspective. *AIDS*, *17*(May), 2407.

Blatt, A. E., & Liebman, S. E. (2013). Drug Induced Acute Kidney Injury. *Hospital Medicine Clinics*, *2*(4), e525–e541.

Bouman, C., & Kellum, J. A. (2010). Acute Dialysis Quality Initiative 2nd International Consensus Conference (pp. 1–12).

Cereza, G., Agusti, A., Pedro´s, C., Vallano, A., Aguilera, C., Dane´s, I., & Arnau, J. M. (2010). Effect of an intervention on the features of adverse drug reactions spontaneously reported in a hospital. *Eur. J. Clin. Pharmacol.*, *66*, 937–945.

Chatterjee, S., Dureja, G. P., Kadhe, G., Mane, A., Phansalkar, A. a., Sawant, S., & Kapatkar, V. (2015). Cross-Sectional Study for Prevalence of Non-Steroidal Anti-Inflammatory Drug-Induced Gastrointestinal, Cardiac and Renal Complications in India: Interim Report. *Gastroenterology Research*, *8*(3-4), 216–221.

Chertow, G., Levy, E., & Hammermeiter, KE. (1998). Independent association between acute renal failure and mortality following cardiac surgery. *JAMA*, *104*(343-348).

Choudhury, D., & Ahmed, Z. (2006). Drug-associated renal dysfunction and injury. *Nat Clin Pract Nephrol*, *2*(2), 80–91.

Conforti, A., Leone, R., Moretti, U., Mozzo, F., & Velo, G. (2001). Adverse Drug Reactions Related to the Use of NSAIDs with a Focus on Nimesulide Results of Spontaneous Reporting from a Northern Italian Area. *Drug Safety*, *24*(14), 1081–1090.

Dasta, J., Goldstein, S., Golper, T., & Schetz, M. (2010). *Acute Dialysis Quality Initiative 4 th International Consensus Conference What are the main factors contributing to iatrogenic kidney injury and how can their impact be minimized?* (pp. 1–26).

Davidman, M., Olson, P., & Kohen, J. (1991). Iatrogenic renal disease. *Arch Intern Med*, *151*, 1809–12.

Davies, E., Green, C., Mottram, D., & Pirmohamed, M. (2006). Adverse drug reactions in hospital in-patients: a pilot study. *J Clin Pharm Ther*, *31*, 335.

Day, R. O., & Graham, G. G. (2013). Non-steroidal anti-inflammatory drugs (NSAIDs). *BMJ (Clinical Research Ed.)*, *346*(June), f3195.

De Mendonca, A., Vincent, J., & Suter, PM. (2000). Acute renal failure in the ICU: risk factors and outcome evaluation by SOFA score. *Intensive Care Medicine*, *26*, 915–21.

Decloedt, E., & Maartens, G. (2011). Drug-induced renal injury, *29*(6), 252–255.

Dhavinjay, P., Misra, A. K., & Varma, S. K. (2013). Diclofenac induced acute renal failure in a decompensated elderly patient. *J Pharmacol Pharmacother*, *4*(2), 155–157.

Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: definitions, diagnosis, and management. *The Lancet*, *356*, 1255–1259.

Evans, R., Lloyd, J., Stoddard, G., Neberker, J., & Samore, M. (2005). Risk factors for adverse drug events: a 10 year analysis. *Annals of Pharmacotherapy*, *39*.

Farcas, A., Sinpetrean, A., Mogosan, C., Palage, M., Vostinaru, O., Bojita, M., & Dumitrascu, D. (2010). Adverse drug reactions detected by stimulated spontaneous reporting in an internal medicine department in Romania. *European Journal of Internal Medicine*, *21*(5), 453–7.

Ferner, R. E., & Butt, T. F. (2008). Adverse drug reactions. *Medicine*, *36*(7), 364–368.

Fintel, B., Samaras, A. T., & Carias, E. (2009, July). The thalidomide tragedy: Lessons for drug safety and regulation. *Helix Magazine*.

Gallelli, L., Colosimo, M., Pirritano, D., Ferraro, M., De Fazio, S., Marigliano, N. M., & De Sarro, G. (2007). Retrospective Evaluation of Adverse Drug Reactions Induced by Nonsteroidal Anti-Inflammatory Drugs. *Clinical Drug Investigation*, *27*(2), 115–122.

Gallelli, L., Ferreri, G., Colosimo, M., Pirritano, D., Guadagnino, L., Pelaia, G., … De Sarro, G. B. (2002). Adverse drug reactions to antibiotics observed in two pulmonology divisions of Catanzaro, Italy: A six-year retrospective study. *Pharmacological Research*, *46*, 395–400.

Ganguli, A., & Prakash, A. (2003). Drug-induced Kidney Diseases. *Journal of the Association of Physicians of India*, *51*(October).

Gholami, K., & Shalviri, G. (1999). Factors associated with preventability, predictability, and severity of adverse drug reactions. *Ann PharmacotherapyPharmacother*, *33*(2).

Glomerulonephritis or nephritis. (2004). In *The Kidney* (pp. 15–16).

Gonzalez-Martin, G., Caroca, C., & Paris, E. (1998). Adverse drug reactions (ADRs) in hospitalized pediatric patients—a prospective study. *Int J Clin Pharmacol Ther*, *36*(10).

Gutthann, S., Rodriguez, L., Raiford, D., & et al. (1996). Nonsteroidal anti-inflammatory drugs and the risk of hospitalization for acute renal failure. *Arch Intern Med*, *156*(21).

Hansen, E. H. (1990). Technology assessment of pharmaceuticals – the necessity of user perspective. *Cah Sociol Demogr Med*, *30*, 313.

Hansen, E. H. (1992). Technology assessment in a user perspective – experiences with drug technology. *Int J Technol Assess Health Care*, *8*(150).

Hassan, Y., Al-ramahi, R. J., Aziz, N. A., & Ghazali, R. (2009). Drug Use and Dosing in Chronic Kidney Disease, *38*(12), 1095–1103.

Hazell, L., & Shakir, S. A. W. (2006). Under-Reporting of Adverse A Systematic Review. *Drug Safety*, *29*(5), 385–396.

Hickey, E. J., Raje, R. R., Reid, V. E., Gross, S. M., & Ray, S. D. (2001). Diclofenac Induced In Vivo Nephrotoxicity May Involved Oxidative Stress-Mediated Massive Genomic DNA Fragmentation and Apoptotic Cell Death. *Free Radical Biology & Medicine*, *31*(2), 139–152.

Hoigne, R., Jaeger, M., Wymann, R., Egli, A., Muller, U., Hess, T., … Kunzi, U. (1990). Time pattern of allergic reactions to drugs. *Agents Actions Suppl*, *29*.

Hörl, W. H. (2010). Nonsteroidal Anti-Inflammatory Drugs and the Kidney. *Pharmaceuticals*, *3*, 2291–2321. doi:10.3390/ph3072291

Horton, R. (2004). Vioxx, the implosion of Merck, and aftershocks at the FDA. *Lancet2*, *364*(9450), 1995.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. (2003). Retrieved from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficac

Jha, V., & Chugh, K. S. (1995). Drug induced renal disease. *J Assoc Physicians India*, *43*, 407.

Jose, J., & Rao, P. G. M. (2006). Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. *Pharmacological Research : The Official Journal of the Italian Pharmacological Society*, *54*(3), 226–33.

Kim, S. Y., & Moon, A. (2012). Drug-induced nephrotoxicity and its biomarkers. *Biomolecules & Therapeutics*, *20*(3), 268–72. doi:10.4062/biomolther.2012.20.3.268

Knauf, H., Bailey, M. A., Hasenfuss, G., & Mutschler, E. (2006). The influence of cardiovascular and antiinflammatory drugs on thiazide-induced hemodynamic and saluretic effects. *Eur. J. Clin. Pharmacol*, *62*.

Kohli, H., Bhaskaran, M., & Muthukumar, T. (2000). Treatment-related acute renal failure in the elderly: a hospital-based prospective study. *Nephrol Dial Transplant.*, *15*(2), 212–217.

Krause, I., Cleper, R., Eisenstein, B., & Davidovits, M. (2005). Acute renal failure, associated with non-steroidal anti-inflammatory drugs in healthy children. *Pediatric Nephrology (Berlin, Germany)*, *20*(9), 1295–8.

Lagnaoui, R., Moore, N., Fach, J., Longy-Boursier, M., & Begaud, B. (2000). Adverse drug reactions in a department of systemic disease-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *Eur. J. Clin. Pharmacol.*, *55*, 181.

Lapi, F., Azoulay, L., Yin, H., Nessim, S. J., & Suissa, S. (2013). Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti- inflammatory drugs and risk of acute kidney injury: nested case-control study. *British Medical Journal*, *346*(December 2015).

Lazarou, J., Pomeranz, B. H., & Corey, P. N. (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA: The Journal of the American Medical Association*, *279*(15), 1200–1205.

Malaysian Guidelines for the Reporting & Monitoring. (2002). Pharmaceutical Services Division, Ministry of Health Malaysia.

Naughton, C. A. (2008). Drug-Induced Nephrotoxicity. *Am Fam Physician*, *78*(6), 743.

Nderitu, P., Doos, L., Jones, P., Davies, S., & Kadam, U. (2013). Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review. *Family Practice*, *30*(3), 247–255.

Nephrotic Syndrome in Adults. (2012, March). *The National Kidney and Urologic Diseases Information Clearinghouse*.

Ng, L. E., Vincent, A. S., Halliwell, B., & Wong, K. P. (2006). Action of diclofenac on kidney mitochondria and cells. *Biochemical and Biophysical Research Communications*, *348*, 494–500.

Official Portal National Pharmaceutical Control Bureau. (2014). Retrieved December 16, 2014, from http://portal.bpfk.gov.my/index.cfm?&menuid=160

Olivier, P., Bertrand, L., Tubery, M., Lauque, D., Montastruc, J. L., & Lapeyre-Mestre, M. (2009). Hospitalizations because of adverse drug reactions in elderly patients admitted through the emergency department. *Drug Aging*, *26*(6), 475.

Passarelli, M., Jacob-Filno, W., & Figueiras, A. (2005). Adverse drug reactions in an elderly hospitalized population. Inappropriate prescription is a leading cause. *Drug Aging*, *22*(9), 767.

Pazhayattil, G. S. (2014). Drug-induced impairment of renal function, 457–468.

Perneger, T. V., Whelton, P. K., & Klag, M. J. (1994). Risk of Kidney Failure Associated with the Use of Acetaminophen , Aspirin , and Nonsteroidal Antiinflammatory Drugs. *New England Journal Med*, *331*(25), 1675–1679.

Pirmohamed, M., & Park, B. K. (2003). Adverse drug reactions: back to the future. *British Journal of Clinical Pharmacology*, *55*, 486.

Ranskov, U. (1999). Glomerular, tubular and interstitial nephritis associated with non-steroidal antiinflammatory drugs. Evidence of a common mechanism. *British Journal of Clinical Pharmacology*, *47*, 203–210.

Rawlins, M., & Thompson, W. (1977). Mechanisms of adverse drug reactions. In D. David (Ed.), *Textbook of adverse drug reactions* (p. 10). New York Oxford University Press.

Rehan, H. S., Arora, T., Kumar, S., & Bhajoni, P. S. (2014). Amikacin and Diclofenac Induced Nephrotoxicity: A Drug-Drug Interaction. *J Rational Pharmacother Res*, *2*(2), 53–55.

Reporting Serious Problems to FDA - What is a Serious Adverse Event? (2014). Retrieved June 04, 2015, from http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm

Rohilla, A., & Yadav, S. (2013). Adverse drug reactions: An Overview. *International Journal of Pharmacological Research*, *3*(1), 1–3.

Rose, V. (1998). Guidelines from the American Geriatric Society target management of chronic pain in older persons. *Am Fam Physician*, *58*(5).

Rosner, M. H., & Okusa, M. D. (2010). Drug-associated acute kidney injury in the intensive care unit.

Schetz, M., Dasta, J., Goldstein, S., & Golper, T. (2005). Drug-induced acute kidney injury. *Curr Opin Crit Care.*, *11*(6).

Schneider, V. (2005). *Association of selective and conventional nonsteroidal anti-inflammatory drugs with acute renal failure*.

Schneider, V., Lévesque, L. E., Zhang, B., Hutchinson, T., & Brophy, J. M. (2006). Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. *American Journal of Epidemiology*, *164*(9), 881–9.

Schoolwerth, A., Sica, D., Ballermann, B., & Wilcox, C. (2001). Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation*, *104*(16), 1985–1991.

Seelig, C. (1992). Changes in residents' attitudes in response to residency program modifications: a prospective study. *South Med. J.*, *85*.

Somers, A., Petrovic, M., Robays, H., & Bogaert, M. (2003). Reporting adverse drug reactions on a geriatric ward: a pilot project. *Eur. J. Clin. Pharmacol.*, *58*, 707.

Stefan, H., Bernatik, J., & Knorr, J. (1999). Visual field defects due to antiepileptic drugs. *Nervenartz*, *70*, 552.

Stergachis, A., Hazlet, T. K., & Boudreau, D. (2008). Pharmacoepidemiology. In *Pharmacotherapy* (pp. 46–55). The McGraw-Hill Companies.

Su, C. H., Hsieh, Y. W., & Gau, C. S. (2007). Spontaneous ADRs Reports of Drug-Induced Renal and Urinary Disorders in Taiwan. *Drug Safety*, *30*(10), 5916.

Suh, D., Woodall, B., Shin, S., & Hermes-De-Santis, E. (2000). Clinical and economic impact of adverse drug reactions in hospitalized patients. *Ann Pharmacotherapy*, *34*.

Thomas, M. (2000). Diuretics, ACE inhibitors and NSAIDs – the triple whammy. *Med J Aust*, *172*, 184–185.

Uchino, S., Kellum, J., & Bellomo, R. (2005). Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*, *294*(7), 813–818.

Veehof, L., Stewart, R., Haaijer-Ruskamp, F., & Jong, B. M. (2000). The development of polypharmacy. A longitudinal study. *Family Practice*, *17*, 261–267.

Waikar, S., Liu, K., & Chertow, G. (2008). Diagnosis, epidemiology and outcomes of acute kidney injury. *Clin J Am Soc Nephrol*, *3*(3), 844–861.

Waring, S. (2006, February). Features and management of drug-induced renal failure. *Prescriber*, (February), 59–63.

Watkins, P. (2000). Review article: COMT inhibitors and liver toxicity. *Neurology*, *55*(11), S53.

Weir, M. R. (2002). Renal effects of nonselective NSAIDs and coxibs. *Cleveland Clinic Journal of Medicine*, *69*(S1), 53–58.

Whelton, A. (1999). Nephrotoxicity of nonsteratoidal anti-inflammatory drugs: physiologic foundations and clinical implications. *Am J Med*, *106*.

Whelton, A., Lefkowith, J. L., West, C. R., & Verburg, K. M. (2006). Cardiorenal effects of celecoxib as compared with the nonsteroidal anti-inflammatory drugs diclofenac and ibuprofen. *Kidney International*, *70*(8), 1495–502.

Whelton, A., & Watson, A. J. (1991). Nonsteroidal Antiinflammatory Drugs: Effects on kidney functions. *J Clin Pharmacol*, *31*(7), 588 – 598.

WHO Adverse Reaction Terminology. (2012). The Upsala Monitoring Centre.

Wyswski, D. K., & Swartz, L. (2005). Adverse drug event surveillance and drug withdrawals in the United States, 1969–2002: the importance of reporting suspected reactions. *Arch Intern Med*, *165*, 1363–1369.

Zager, R. . (1997). Pathogenetic mechanisms in nephrotoxic acute renal failure. *Semin Nephrol*, *17*(1), 3–14.

APPENDICES

APPENDIX I: Approval Letter from MREC Secretariat

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 KUALA LUMPUR

Tel.: 03-2287 4032/2282 0491/2282 9085
03-2282 9082/2282 1402/2282 1449
Faks: 03-2282 0015

Ruj. Kami : (5) KKM/NIHSEC/P15-1209
Tarikh : 6hb Oktober 2015

NURULMAYA BINTI AHMAD SA'AD
UNIVERSITI TEKNOLOGI MARA (UITM) – PUNCAK ALAM CAMPUS

Tuan/Puan,

NMRR-15-1325-26886
ANALYSIS OF ADVERSE DRUG REACTIONS RELATED TO DRUG-INDUCED RENAL INJURY BASED ON SPONTANEOUS ADVERSE DRUG REACTIONS REPORTING IN MALAYSIA 2010 - 2014

Lokasi Kajian: NATIONAL PHARMACEUTICAL CONTROL BUREAU (NPCB)

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) tiada halangan, dari segi etika, ke atas pelaksanaan kajian tersebut. JEPP mengambil maklum bahawa kajian tersebut hanya melibatkan pengumpulan data menggunakan data sekunder sahaja.

3. Segala rekod dan data subjek adalah **SULIT** dan hanya digunakan untuk tujuan kajian ini dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pegawai Kesihatan Daerah/Pengarah Hospital dan Ketua-Ketua Jabatan atau pegawai yang bertanggung jawab disetiap lokasi kajian di mana kajian akan dijalankan mesti diperolehi sebelum kajian dijalankan. Tuan/Puan perlu akur dan mematuhi keputusan tersebut.

4. Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga **5hb Oktober 2016**. Tuan/Puan perlu menghantar dokumen-dokumen seperti berikut selepas mendapat kelulusan etika . Borang-borang berkaitan boleh dimuat turun daripada laman web MREC (http://www.nih.gov.my/mrec).

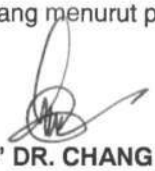
I. *'Continuing Review Form'* selewat-lewatnya 2 bulan sebelum tamat tempoh kelulusan ini bagi memperbaharui kelulusan etika.
II. Laporan tamat kajian pada penghujung kajian.
III. Laporan mengenai "*All adverse events, both serious and unexpected*"/*Protocol Deviation* atau *Violation* kepada Jawatankuasa Etika & Penyelidikan Perubatan, KKM jika berkenaan.
IV. Memaklumkan jika terdapat pindaan keatas sebarang dokumen kajian.

5. Sila ambil maklum bahawa sebarang urusan surat-menyurat berkaitan dengan penyelidikan ini haruslah dinyatakan nombor rujukan surat ini untuk melicinkan urusan yang berkaitan.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,



(DATO' DR. CHANG KIAN MENG)
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

CC

Pengarah
National Pharmaceutical Control Bureau (NPCB)

APPENDIX II: Permission Letter from National Pharmaceutical Control Bureau

BIRO PENGAWALAN FARMASEUTIKAL KEBANGSAAN
NATIONAL PHARMACEUTICAL CONTROL BUREAU
Kementerian Kesihatan Malaysia
Ministry of Health Malaysia
Lot 36 Jalan Universiti
46200 Petaling Jaya
Selangor Darul Ehsan
MALAYSIA

Tel. : +603-7883 5400
Faks (*Fax*) : +603-7956 2924
Laman Web (*Web*) : www.bpfk.gov.my

Ruj kami : (3) dlm.BPFK/17/FV/2 Jld 17
Tarikh : 20 Ogos 2015

Professor Dr.Noorizan Abd. Aziz
Jabatan Amalan Farmasi/Farmasi Klinikal
Fakulti Farmasi, Universiti Teknologi Mara
Kampus Puncak Alam
42300 Bandar Puncak Alam
Selangor

Puan,

PERMOHONAN MENJALANKAN KAJIAN PENYELIDIKAN SARJANA DI BIRO PENGAWALAN FARMASEUTIKAL KEBANGSAAN (BPFK)

Saya dengan hormatnya merujuk kepada perkara di atas dan surat puan bertarikh 12 Ogos 2015.

2. Pihak kami tiada halangan di atas permohonan puan bagi membenarkan pelajar Sarjana Amalan Farmasi, Nurulmaya Binti Ahmad Sa'ad (No. KP: 840913145290) untuk mengumpul data di BPFK bagi menjalankan kajian bertajuk ***'Analysis of Adverse Drug Reactions Related To Drug Induced Renal Injury Based on Spontaneous Adverse Drug Reactions Reporting in Malaysia 2010-2014'*** bermula dari September 2015 hingga November 2015.

3. Adalah dimaklumkan bahawa kebenaran ini dan maklumat yang diperolehi adalah untuk tujuan penyelidikan sahaja dan sebarang penerbitan ke atas hasil kajian ini oleh pelajar tersebut perlu mendapat kelulusan pihak Kementerian Kesihatan Malaysia terlebih dahulu.

4. Pihak puan juga diminta membuat kenyataan penghargaan kepada Pusat Pemonitoran Kesan Advers Ubat Kebangsaan, BPFK di dalam sebarang bentuk penerbitan hasil kajian tersebut dan salinan laporan dikemukakan kepada pihak kami untuk tujuan rekod dan fail.

5. Perhatian pihak puan mengenai perkara ini adalah dihargai.

Sekian, terima kasih.

'BERKHIDMAT UNTUK NEGARA'

Saya yang menurut perintah,

(TAN ANN LING)
Pengarah Farmasi Regulatori
Biro Pengawalan Farmaseutikal Kebangsaan
Kementerian Kesihatan Malaysia

sk. Dekan Fakulti Farmasi
Universiti Teknologi Mara

ir/ssar

2

APPENDIX III: Investigator's Agreement, Head of Department and Organisational / Institutional Approval

Ver 3.0 September 2014 *NMRR/FORM/IAHODIA*

INVESTIGATOR'S AGREEMENT, HEAD OF DEPARTMENT AND ORGANISATIONAL / INSTITUTIONAL APPROVAL
PERSETUJUAN PENYELIDIK DAN KEBENARAN KETUA JABATAN DAN PENGARAH ORGANISASI/INSTITUSI

This document is intended for online submission for formal research registration. It is issued as the Investigator's Agreement to participate in the research as well as the investigator's **Head of Department and Director's Approval**. Please upload this document in the required section in NMRR upon completion.
**Note: This form is NOT to be used for obtaining permission to conduct the research at the named / selected study site(s).

*Dokumen ini adalah untuk penghantaran 'online' mengikut prosedur rasmi pendaftaran penyelidikan. Borang ini dikeluarkan sebagai pengakuan penyelidik untuk menjalankan penyelidikan dan persetujuan serta kebenaran daripada **Ketua Jabatan dan Pengarah masing-masing**. Sila lengkapkan borang ini dan memuat naik ke dalam sistem NMRR di seksyen yang telah ditetapkan.*
***Nota : Borang ini BUKAN digunakan untuk tujuan mendapatkan keizinan untuk menjalankan penyelidikan di lokasi kajian yang dipilih.*

Research Title *[Tajuk Penyelidikan]*	ANALYSIS OF ADVERSE DRUG REACTIONS RELATED TO DRUG-INDUCED RENAL INJURY BASED ON SPONTANEOUS ADVERSE DRUG REACTIONS REPORTING IN MALAYSIA 2010 - 2014		
Research ID *[Nombor Pendaftaran]*	26886	**Protocol Number (if available)** *[Nombor Protokol (jika ada)]*	

INVESTIGATOR'S AGREEMENT *[PERSETUJUAN PENYELIDIK]*

I have understood the above mentioned proposed research and I agree to participate as an investigator and being responsible to conduct the research.

Saya faham atas cadangan penyelidikan di atas dan bersetuju untuk mengambil bahagian serta bertanggungjawab untuk melaksanakan penyelidikan tersebut.

Name *[Nama]*	Noorizan Binti Abd.Aziz
IC number *[Nombor K/P]*	570513086968
Institute *[Institusi]*	UNIVERSITI TEKNOLOGI MARA (UITM) - PUNCAK ALAM CAMPUS
Signature and Official stamp *[Tandatangan dan Cop Rasmi]*	Prof. Dr Noorizan Abd Aziz B. Pharm, M. Sc (Radiopharmacy), Phar... D. (USA) Faculty of Pharmacy, University Teknologi MARA (UITM) Puncak Alam Campus, 42300 Puncak Alam, Selangor Darul Ehsan, MALAYSIA. Tel (Office): +60313258 4835
Date *[Tarikh]*	11/8/2015

HEAD OF DEPARTMENT AGREEMENT *[PERSETUJUAN KETUA JABATAN]*

I agree to allow the above named investigator to conduct the above titled research.

Saya bersetuju dan membenarkan pegawai seperti bernama di atas untuk menjadi penyelidik di dalam projek penyelidikan tersebut di atas.

Name of Head : *[Nama Ketua Jabatan]*	
Signature and Official stamp *[Tandatangan dan Cop Rasmi]*	Profesor Dr. Yahaya Hassan K ...ua, Pusat Pengajian Amalan Farmasi Fakulti Farmasi Universiti Teknologi Mara(UITM) Kampus Puncak Alam 42300 Puncak Alam Tel: +603-3258 4834 11/8/2015
Date *[Tarikh]*	

ORGANISATIONAL / INSTITUTIONAL APPROVAL *[KEBENARAN ORGANISASI / INSTITUSI]*

I acknowledge and approve the named officer to conduct the above titled research.

Saya mengesahkan dan mengambil maklum penglibatan pegawai ini di dalam penyelidikan tersebut.

Name of Director *[Nama Pengarah]*	
Signature and Official stamp *[Tandatangan dan Cop Rasmi]*	DR. NORAMLIZAN RAMLI Timbalan Dekan (Akademik & Kualiti) Fakulti Farmasi UiTM, Kampus Puncak Alam 42300 Bandar Puncak Alam Selangor
Date *[Tarikh]* 11/8/2015	

This is computer generated. Borang ini adalah cetakan komputer. [26886/11271/100259]

Ver 3.0 September 2014 *NMRR/FORM/IAHODIA*

INVESTIGATOR'S AGREEMENT, HEAD OF DEPARTMENT AND ORGANISATIONAL / INSTITUTIONAL APPROVAL
PERSETUJUAN PENYELIDIK DAN KEBENARAN KETUA JABATAN DAN PENGARAH ORGANISASI/INSTITUSI

This document is intended for online submission for formal research registration. It is issued as the Investigator's Agreement to participate in the research as well as the investigator's **Head of Department and Director's Approval**. Please upload this document in the required section in NMRR upon completion.
**Note: This form is NOT to be used for obtaining permission to conduct the research at the named / selected study site(s).

*Dokumen ini adalah untuk penghantaran 'online' mengikut prosedur rasmi pendaftaran penyelidikan. Borang ini dikeluarkan sebagai pengakuan penyelidik untuk menjalankan penyelidikan dan persetujuan serta kebenaran daripada **Ketua Jabatan dan Pengarah masing-masing**. Sila lengkapkan borang ini dan memuat naik ke dalam sistem NMRR di seksyen yang telah ditetapkan.*
***Nota : Borang ini BUKAN digunakan untuk tujuan mendapatkan keizinan untuk menjalankan penyelidikan di lokasi kajian yang dipilih.*

Research Title *[Tajuk Penyelidikan]*	ANALYSIS OF ADVERSE DRUG REACTIONS RELATED TO DRUG-INDUCED RENAL INJURY BASED ON SPONTANEOUS ADVERSE DRUG REACTIONS REPORTING IN MALAYSIA 2010 - 2014		
Research ID *[Nombor Pendaftaran]*	26886	**Protocol Number (if available)** *[Nombor Protokol (jika ada)]*	

INVESTIGATOR'S AGREEMENT *[PERSETUJUAN PENYELIDIK]*

I have understood the above mentioned proposed research and I agree to participate as an investigator and being responsible to conduct the research.

Saya faham atas cadangan penyelidikan di atas dan bersetuju untuk mengambil bahagian serta bertanggungjawab untuk melaksanakan penyelidikan tersebut.

Name *[Nama]*	ROKIAH BINTI ISAHAK
IC number *[Nombor K/P]*	610109715068
Institute *[Institusi]*	NATIONAL PHARMACEUTICAL CONTROL BUREAU (NPCB)
Signature and Official stamp *[Tandatangan dan Cop Rasmi]*	ROKIAH BINTI ISAHAK Ketua Penolong Pengarah Kanan Pusat Pasca Pendaftaran Produk Biro Pengawalan Farmaseutikal Kebangsaan Petaling Jaya
Date *[Tarikh]*	27/8/15

HEAD OF DEPARTMENT AGREEMENT *[PERSETUJUAN KETUA JABATAN]*

I agree to allow the above named investigator to conduct the above titled research.

Saya bersetuju dan membenarkan pegawai seperti bernama di atas untuk menjadi penyelidik di dalam projek penyelidikan tersebut di atas.

Name of Head : *[Nama Ketua Jabatan]*	
Signature and Official stamp *[Tandatangan dan Cop Rasmi]*	SAMEERAH BT SHAIKH ABD. RAHMAN Timbalan Pengarah Pusat Pasca Pendaftaran Produk Biro Pengawalan Farmaseutikal Kebangsaan Petaling Jaya
Date *[Tarikh]*	28/8/2015

ORGANISATIONAL / INSTITUTIONAL APPROVAL *[KEBENARAN ORGANISASI / INSTITUSI]*

I acknowledge and approve the named officer to conduct the above titled research.

Saya mengesahkan dan mengambil maklum penglibatan pegawai ini di dalam penyelidikan tersebut.

Name of Director *[Nama Pengarah]*	
Signature and Official stamp *[Tandatangan dan Cop Rasmi]*	TAN ANN LING Pengarah Regulatori Farmasi Biro Pengawalan Farmaseutikal Kebangsaan Kementerian Kesihatan Malaysia Petaling Jaya
Date *[Tarikh]*	2/9/2015

This is computer generated. Borang ini adalah cetakan komputer. [26886/2641/14915]

INVESTIGATOR'S AGREEMENT, HEAD OF DEPARTMENT AND ORGANISATIONAL / INSTITUTIONAL APPROVAL
PERSETUJUAN PENYELIDIK DAN KEBENARAN KETUA JABATAN DAN PENGARAH ORGANISASI/INSTITUSI

This document is intended for online submission for formal research registration. It is issued as the Investigator's Agreement to participate in the research as well as the investigator's **Head of Department and Director's Approval**. Please upload this document in the required section in NMRR upon completion.
**Note: This form is NOT to be used for obtaining permission to conduct the research at the named / selected study site(s).

*Dokumen ini adalah untuk penghantaran 'online' mengikut prosedur rasmi pendaftaran penyelidikan. Borang ini dikeluarkan sebagai pengakuan penyelidik untuk menjalankan penyelidikan dan persetujuan serta kebenaran daripada **Ketua Jabatan dan Pengarah masing-masing**. Sila lengkapkan borang ini dan memuat naik ke dalam sistem NMRR di seksyen yang telah ditetapkan.*
***Nota : Borang ini BUKAN digunakan untuk tujuan mendapatkan keizinan untuk menjalankan penyelidikan di lokasi kajian yang dipilih.*

Research Title *[Tajuk Penyelidikan]*	ANALYSIS OF ADVERSE DRUG REACTIONS RELATED TO DRUG-INDUCED RENAL INJURY BASED ON SPONTANEOUS ADVERSE DRUG REACTIONS REPORTING IN MALAYSIA 2010 - 2014		
Research ID *[Nombor Pendaftaran]*	26886	**Protocol Number (if available)** *[Nombor Protokol (jika ada)]*	

INVESTIGATOR'S AGREEMENT *[PERSETUJUAN PENYELIDIK]*

I have understood the above mentioned proposed research and I agree to participate as an investigator and being responsible to conduct the research.
Saya faham atas cadangan penyelidikan di atas dan bersetuju untuk mengambil bahagian serta bertanggungjawab untuk melaksanakan penyelidikan tersebut.

Name *[Nama]*	Nurulmaya Binti Ahmad Sa'ad
IC number *[Nombor K/P]*	840913145290
Institute *[Institusi]*	UNIVERSITI TEKNOLOGI MARA (UITM) – PUNCAK ALAM CAMPUS
Signature and Official stamp *[Tandatangan dan Cop Rasmi]*	
Date *[Tarikh]*	11/8/2015

HEAD OF DEPARTMENT AGREEMENT *[PERSETUJUAN KETUA JABATAN]*

I agree to allow the above named investigator to conduct the above titled research.
Saya bersetuju dan membenarkan pegawai seperti bernama di atas untuk menjadi penyelidik di dalam projek penyelidikan tersebut di atas.

Name of Head : *[Nama Ketua Jabatan]*	
Signature and Official stamp *[Tandatangan dan Cop Rasmi]*	Profesor Dr.Yahaya Hassan Ketua,Pusat Pengajian Amalan Farmasi Fakulti Farmasi Universiti Teknologi Mara(UITM) Kampus Puncak Alam 42300 Puncak Alam Tel:+603-3258 4834
Date *[Tarikh]*	11/8/2015

ORGANISATIONAL / INSTITUTIONAL APPROVAL *[KEBENARAN ORGANISASI / INSTITUSI]*

I acknowledge and approve the named officer to conduct the above titled research.
Saya mengesahkan dan mengambil maklum penglibatan pegawai ini di dalam penyelidikan tersebut.

Name of Director *[Nama Pengarah]*	
Signature and Official stamp *[Tandatangan dan Cop Rasmi]*	DR. AMLIZAN RAMLI Timbalan Dekan (Akademik & Kualiti) Fakulti Farmasi UiTM, Kampus Puncak Alam 42300 Bandar Puncak Alam Selangor
Date *[Tarikh]*	11/8/2015

This is computer generated. Borang ini adalah cetakan komputer. [26886/36226/2650]

APPENDIX IV: Ethics Approval by UiTM Ethics Committee

www.irmi.uitm.edu.my

Institut Pengurusan Penyelidikan & Inovasi
Institute of Research Management & Innovation

Universiti Teknologi MARA
Aras 3, Bangunan Wawasan
40450 Shah Alam, Selangor, MALAYSIA
Tel: (+603) 5544 2094/2090
Faks: (+603) 5544 2096/2767
E-mel: irmiuitm@salam.uitm.edu.my

UNIVERSITI TEKNOLOGI MARA

Reference : 600-RMI (5/1/6)
Our reference : REC/106/15
Date : 22 October 2015

Professor Dr Noorizan Abd Aziz
Faculty of Pharmacy
Universiti Teknologi MARA (UiTM)
Puncak Alam Campus
42300 Bandar Puncak Alam
Selangor

Dear Professor Dr Noorizan,

ETHICS APPROVAL BY UiTM RESEARCH ETHICS COMMITTEE – Analysis of Adverse Drug Reactions Related to Drug-Induced Renal Injury Based on Spontaneous Adverse Drug Reactions Reporting in Malaysia 2012-2014

Thank you for your research ethics application on 21 October 2015. We would like to inform that the UiTM Research Ethics Committee had deliberated your proposal.

The REC members attending the above meeting are shown below:

Name	REC Membership	Designation
Professor Dr Hadariah Bahron	Chairman	Assistant Vice Chancellor, Institute of Research Management & Innovation (IRMI), UiTM
Professor Dato' Dr Khalid Yusoff	Member	Vice Chancellor and President, UCSI University
Dato' Mohamed Dahan Abdul Latiff	Member	Chairman, Flight Solutions Sdn. Bhd
Professor Dr Zainuddin Merican Md Hashim Merican	Member	Professor, College University Medical Science (Pharmacology)
Professor Dr Syed Hassan Syed Ahmad Almashoor	Member	Professor, Faculty of Medicine, UiTM
Associate Professor Dr Jamaluddin Mahmud	Member	Deputy Dean, Faculty of Mechanical Engineering, UiTM
Dr Aimi Nadia Mohd Yusof	Secretary	Research Ethics Coordinator, Institute of Research Management & Innovation (IRMI), UiTM

It is our pleasure to inform you that the Research Ethics Committee has agreed to grant an ethics approval for the said study.

Please submit progress report of the study to the REC Secretariat 12 months (1 year) after the date of approval letter.

The UiTM Research Ethics Committee operates in accordance to the ICH Good Clinical Practice Guidelines, Malaysia Good Clinical Practice Guidelines and the Declaration of Helsinki.

Thank you.

Yours truly,

PROFESSOR DR HADARIAH BAHRON
Assistant Vice Chancellor (Research & Innovation)
Chairman of UiTM Research Ethics Committee

c.c.: Dean
Faculty of Pharmacy
Universiti Teknologi MARA (UiTM)
Puncak Alam Campus
42300 Bandar Puncak Alam
Selangor

Nurulmaya Ahmad Sa'ad
Faculty of Pharmacy
Universiti Teknologi MARA (UiTM)
Puncak Alam Campus
42300 Bandar Puncak Alam
Selangor

Rokiah Isahak
Faculty of Pharmacy
Universiti Teknologi MARA (UiTM)
Puncak Alam Campus
42300 Bandar Puncak Alam
Selangor

APPENDIX V: Similarity Index (Turnitin)

turnitin Originality Report

Dissertation Write Up - Drug Induced Renal In...

By Nurulmaya Ahmad Sa'ad

Similarity Index 11%

Similarity by Source

Internet Sources: 3%
Publications: 12%
Student Papers: 3%

INSTITUTE OF GRADUATE STUDIES UNIVERSITI TEKNOLOGI MARA ANALYSIS OF ADVERSE DRUG REACTIONS RELATED TO DRUG-INDUCED RENAL INJURY BASED ON SPONTANEOUS ADVERSE DRUG REACTIONS REPORTING IN MALAYSIA 2010 - 2014 NURULMAYA BINTI AHMAD SA'AD Dissertation submitted in partial fulfillment of the requirements for the degree of Master of Clinical Pharmacy Faculty of Pharmacy January 2016 CHAPTER 3 METHODOLOGY 3.1 Research Design and Location of the Study This is a retrospective study where the data was collected at the Pharmacovigilance Section, Centre of Post Registration Product, National Pharmaceutical Control Bureau (NPCB). This study is descriptive in nature and relies on existing data. The data under observation are quantitative in nature. As stated in the "International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use" (2003), a report in which unsolicited or voluntary contact is made between a regulatory agency and a reporter is a spontaneous report. According to the ICH guidelines, there are a few minimum reporting criteria for an ADR to be accepted and they include identifiable reporter, patient, at least one adverse event and one suspected drug or product. 3.2 Sample Size Calculation For the purpose of this study, a sample size was not calculated as all spontaneous ADR reports from 2010 to 2014 related to the renal disorders were extracted from the Quest 2 database, regardless of the seriousness. Patient demographics, drug treatment and types of renal injuries were identified and recorded. 3.3 Validity of Data Collection In order to ensure the validity of data collection, ten (10) reports were initially sampled from the Quest 2 database (computerised data) and these data were compared (crosschecked) with the data from the original reports (hardcopy or softcopy form sent by the reporters). Data clarification with the experts or person- in- charge was also done. When there was some conflicts in the data (at least in one sample), another ten (10) reports were sampled. This process continued until all ten (10) sampled reports have no conflicts and in accordance with the original data. Once there was no discrepancy or conflict between those two softcopy and hardcopy data in any of the samples, the report sampling process was then stopped. 3.4 Study Flow Chart Retrieved ADR reports related to drug induced renal injury from Quest 2 Collected/extracted data for individual reports If incomplete, original ADR report form has been searched (hand search) Compiled and analysed data Discussion and final write-up Figure 3.1: Flow chart of the study process 3.5 Ethical Consideration The approval to commence this study was endorsed by the Research Ethics Committee (REC) of Universiti Teknologi MARA (UiTM) in order to ensure that the research project is conducted in compliance with the national and international conditions and guidelines stipulated in the Good Clinical Practice Guideline, Ministry of Health (MOH), Malaysia and the Declaration of Helsinki, World Medical Association (WMA).An approval from the Research and Ethics Committee (MREC) of the Malaysian Ministry of Health was also obtained as this project will be conducted in the facilities of MOH. Furthermore, this study was registered under National Medical Research Registry (NMRR), approved by the Clinical Research Centre (CRC) Ministry of Health Malaysia and was given with registration ID NMRR-15-203-24512. A formal letter was given by the pharmacy faculty, UiTM to the Director of Regulatory Pharmacy, National Pharmaceutical Control Bureau before the study was conducted. All the data that were obtained from the Quest 2 database such as patients' profile and medical records were restricted only for the investigators and were ensured to be kept private and confidential. 3.6 Data Collection

1 4% match (publications) Jose, J., "Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital", Pharmacological Research, 200609

2 3% match (publications) Clinical Nephrotoxins, 1998.

3 2% match (publications) Anita Conforti, "Adverse Drug Reactions Related to the Use of NSAIDs with a Focus on Nimesulide", Drug Safety, 2001

4 1% match (Internet from 09-Jun-2014) http://www.gustrength.com

5 1% match (publications) Clinical Nephrotoxins, 2008.

6 1% match (publications) C H Su, "Spontaneous ADRs Reports of Drug-Induced Renal and Urinary Disorders

APPENDIX VI: Gantt Chart for Research Study

2015/2016		JUNE				JULY				AUGUST				SEPTEMBER				OCTOBER			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Research area identification	Planned																				
	Achieved																				
First draft proposal	Planned																				
	Achieved																				
Literature review	Planned																				
	Achieved																				
Second draft proposal	Planned																				
	Achieved																				
Final Proposal Submission/Defence Research Proposal (DRP)	Planned																				
	Achieved																				
Data collection	Planned																				
	Achieved																				
SPSS data entry	Planned																				
	Achieved																				
Data analyses	Planned																				
	Achieved																				
2015/2016		NOVEMBER				DECEMBER				JANUARY				FEBRUARY							
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4				
Thesis write-up	Planned																				
	Achieved																				
Thesis presentation	Planned																				
	Achieved																				
Correction and submission	Planned																				
	Achieved																				

AUTHOR'S PROFILE

PERSONAL PARTICULAR

Name : Nurulmaya Binti Ahmad Sa'ad

Address : No. 32A, Jalan Sanggul 2, Bandar Puteri, 41200 Klang, Selangor

Email : mayasaad_84@yahoo.com

Gender : Female

Date of Birth : 13th September 1984

Citizenship : Malaysian

EDUCATIONAL BACKGROUND

2013 – 2014 : Universiti Teknologi MARA (UiTM), Puncak Alam Campus.

Student of Masters in Pharmacy Practice

2004 – 2008 : International Islamic University Malaysia (IIUM), Kuantan Campus.

Bachelor of Pharmacy (Honours)

2002 – 2004 : Matriculation Centre, International Islamic University Malaysia (IIUM).

1997 – 2001 : Sek. Men. Kebangsaan Tengku Ampuan Rahimah, Klang (Form 1-Form 5)

Sijil Pelajaran Malaysia (2001)

WORKING EXPERIENCES

Position	Institution/Employer	Duration
Full Registered Pharmacist (FRP) / Pharmacist	Pejabat Kesihatan Daerah Klang	August 2009 - present
Provisional Registered Pharmacist (PRP)	National Pharmaceutical Control Bureau (NPCB)	August 2008 – August 2009