A PHARMACOINFORMATIC PREDICTION MODEL FOR ADVERSE DRUG REACTIONS

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Study terminology

Patient ADR number; is the total number of patients with specific factors having a specific ADR in each medical literature.

Category; is the classification of the main patient's factors which affect the development of ADRs.

Patient factors; is the sub classification of categories; e.g. sex is further classified into male and female. It is written exactly as it appears in the medical literature and is considered unchanged original data.

Variables; is the re-classified factors. Factors are classified into specific ranges and groups in order to obtain a figure suitable for calculation by the model.

Variable number; is the number of patients in a specific variable.

Normalization; is the process that makes something more normal, which typically means, conforming to some regularity or rule, or returning from some state of abnormality. Normalization of a function (in general mathematics) is the process of removing a discontinuity. Normalized patients; is assumed to be 1000 in this research.

Normalized factor; {normalization number "1000"/study patient number}. For further details, refer to normalization.

Normalized factor patients; Normalized Factor Patients = [Normalized Factor]*[Factor Patient No].

Normalized ADR patients; [Normalized Factor]*[Patient ADR No].

Percentage of ADR patients; total normalized ADR patients/ total normalized factor patients * 100%

ABSTRAK

Teknologi maklumat telah menjadi sebahagian daripada ilmu pengetahuan dalam bidang sains. Penelitian saintis bersama ahli akademik secara serius berfikir tentang perlunya teknologi maklumat dalam ilmu farmasi termasuk farmasi klinikal dan penjagaan farmaseutikal. Teknologi maklumat telah diterapkan secara tidak langsung dalam proses penemuan perubatan dan rawatan pesakit untuk jangka masa yang panjang. Farmasi informatik melibatkan kajian, rekabentuk, dan pelaksanaan maklumat dan sistem maklumat farmasi. Pembangunan pengkalan data secara berkomputer on preskripsi diatas talian dan data data maklmal telah meningkatkan kemampuan institusi institusi dan organisasi kesihatan untuk meneliti kesan advers (ADR) yang kerap berlaku. Kajian ini mempunyai empat tujuan utama; Objektif pertama adalah untuk membangunkan model secara matematik untuk mengira peratusan kemungkinan berlakunya ADR menggunakan maklumat yang berkaitan dengan pesakit. Objektif kedua adalah untuk menilai kewujudan maklumat penting dalam literatur perubatan yang sedia ada menggunakan model ramalan ADR. Objektif ketiga adalah untuk menguji fungsi model tersebut. Keempat objektifnya adalah untuk melakukan proses validasi bagi memastikan fungsinya untuk menjangkakan kesan ADR. Literatur perubatan yang berkaitan dengan keselamatan dan efikasi drug antihipertensi digunakan sebagai sumber maklumat. Maklumat ini merangkumi semua data yang berkaitan pesakit dan rawatannya. Data ini memainkan peranan penting dalam pembangunan model ADR ini. Pengiraan ini bergantung pada koleksi data yang berkaitan dengan pesakit yang akan mempengaruhi berlakunya kesan ADR ini. Untuk mengoptimalkan maklumat yang dikumpul daripada literatur yang diperolehi, pengkelasan berdasarkan

faktor pesakit dilakukan untuk pengiraan yang tepat. Microsoft akses digunakan untuk model struktur dan pembangunan. Selepas kemasukan data, maklumat yang dikumpul akan dianalisis untuk sebarang maklumat yang hilang. Analisis ini dilakukan menggunakan Microsoft akses dan program SPSS. Pengujian model dilakukan dengan menghasilkan laporan tentang ADR untuk drug antihipertensi. Laporan ini selektif untuk drug drug dan faktor-faktor pesakit yang tertentu. Validasi model diperolehi dengan kajian perbandingan antara peratusan ADR untuk Amlodipine yang dihitung daripada model dan kadar sebenar berlakunya ADR daripada rekod perubatan pesakit di hospital. Paduan t-test untuk variabel independen digunakan untuk pengujian dengan 95% *confidence interval*. Keputusan akhir kajian ini adalah pengembangan konsep baru untuk jangkaan ADR. Model ini akan menghitung kadar peratusan minimum dan maksimum berlakunya ADR dalam pesakit yang spesifik. Analisis data tentang maklumat yang hilang dalam literatur perubatan membawa masalah ini menjadi perhatian. Banyak maklumat yang hilang termasuk berkaitan dengan pesakit, rawatan dan ADR. Model ini juga diuji untuk kefungsian dengan menganalisis beberapa drug antihipertensi berlakunya ADR. Tidak ada perbezaan yang signifikan secara statistik (nilai p 0,46) antara peratusan ADR Amlodpine daripada pesakit dan yang dikira dengan menggunakan model ramalan ADR. Pemanfaatan teknologi maklumat menyediakan masa depan yang lebih cerah yang dalam penggunaan drug dan membantu dalam membuat keputusan dalam pemilihan drug yang sesuai. Kajian ini mengembangkan pendekatan baru untuk farmakoinfomatik klinikal untuk menjangkakan berlakunya ADR.

Abstract

Information technology has become part of all kinds of sciences. Research scientists along with the academicians are seriously thinking about the need of information technology in pharmaceutical sciences including clinical pharmacy and pharmaceutical care. Information technology has been applied indirectly in the medication discovery process and patient care for a long period of time. Pharmacy Informatics involves the study, design, and implementation of information and information systems in Pharmacy. The development of computerized prescriptions and laboratory databases has greatly enhanced the ability of institutions and organizations to screen for known adverse drug reactions (ADR). This research has four main objectives; first objective is to develop a mathematical model to calculate the percentage of possible occurrence of ADRs using patients related information. Second objective is to evaluate the availability of essential information in medical literature using the ADR prediction model. Third objective is to test the model for its functionality. Fourth objective is to validate the model. Medical literature on antihypertensive medication safety and efficacy is used as a source of information. This information includes all patient related and medication related data. These data play an important role in the development of ADRs. The calculation depends on the collection of patient related factors which affect the development of the ADRs. For the optimal utilization of information collected from literature, classification of patient factors is done for proper calculation. Microsoft access is used for model structure and development. After data entry, information collected from literature were analyzed for missing information. The analysis was done using Microsoft access and SPSS programmes. Testing the model is accomplished by

generating reports on ADRs for antihypertensive medications. These reports are selective for certain medications and certain patients factors. Model validation was achieved by a comparative study between the percentage of ADRs for Amlodipine calculated from the model and the actual occurrence of ADRs from hospital patients medical records. Paired t-test for independent variables is used for testing with confidence interval of 95%. The end product of this research is the development of a new concept for the prediction of ADRs. This model calculates the minimum and the maximum percentage of ADR occurrence in specific patient. Data analysis regarding missing information in medical literature brought this problem into attention. Many kinds of information are missing including patient, medication and ADR related information. The model is also tested for its functionality by analyzing some of the antihypertensive medications for their ADR occurrence. There is no statistically significant difference (p value 0.46) between ADR percentage of Amlodpine from actual patients and the calculated ones using ADR prediction model. The utilization of information technology provides a promising future for the safe use of medications and helps in medical decision making and proper medication selection. This study develops a new clinical pharmacoinformatics approach for the prediction of ADRs.

Chapter 1

Introduction

1.1. Background

1.1.1. Adverse Drug Reactions (ADRs)

Safety issues arise whenever medical choices have to be made (Bauer, 2008). ADRs can occur in all settings where healthcare is provided. Most of the current evidence comes from hospitals because the risks associated with hospital treatment are higher (Yurdaguel, *et al*., 2008). Many such events occur in other healthcare settings such as consulting rooms, nursing homes, pharmacies, community clinics and patients' homes (Handler, *et al*., 2008).

While the drug discovery process has been revolutionized by new techniques, drug safety assessment lags well behind and is still reliant on many of the same technologies that have been used for several decades (Powley, *et al*., 2009). Current conceptual thinking on the safety of patients places the prime responsibility for ADRs on deficiencies in system design, organization and operation - rather than on individual practitioners or products. Berwick and Leape, (1999) recommended that checks and quality assurance should be built into the use system, rather than assuming that all will be well.

By the time a drug is marketed, only about 1500 patients may have been exposed to the drug. Thus, only those ADRs occurring at a frequency of greater than 1 in 500 will have been identified at the time of licensing (Andrade, *et al*., 2007). Pirmohamed, *et al*. (1998) suggested that the assessment of ADRS therefore is likely to represent an important aspect of drug therapy. Silverman, *et al*. (2003) showed that the overall rate of ADRs is estimated to be 6.5 per 100 admissions; 28% of these reactions are preventable.

Once put onto the market, a drug leaves the secure and protected scientific environment of clinical trials and is legally set free for consumption by the general population (Russell, *et al*., 1992). At this point, most drugs will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals.

In order to prevent or reduce harm to patients and thus improve their health, mechanisms for evaluating and monitoring the safety of drugs in clinical use are vital. In practice this means having in place a well-organized pharmacovigilance system. Pharmacovigilance - an umbrella term used to describe the processes for monitoring and evaluating ADRs is a key component of effective drug regulation systems, clinical practice and public health programmes.

The World Health Organization [WHO], (2003) defines pharmacovigilance as the science and activity relating to the detection, assessment, understanding and prevention of ADRs or any other drug related problem. The most important task of the WHO International Drug Monitoring is to identify ADR signals of drug safety problems as early as possible. Events such as the thalidomide tragedy highlight the extreme importance of effective drug monitoring systems for all drugs (Neubert, *et al*., 1995). The principal aims of pharmacovigilance programmes are:

• To improve patient care and safety in relation to the use of drugs, and all medical and paramedical interventions;

• To improve patient health and safety in relation to the use of drugs;

• To contribute to the assessment of benefit, harm, effectiveness and risk of drugs, encouraging their safe, rational and more effective (including cost-effective) use;

• To promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public.

1.1.2. Pharmacoinformatics

Both in science and in healthcare, methods of thinking and actions are dominated by man-made rules or laws that have been discovered and theories that have been developed in the course of scientific research. Computers facilitate the process of structuring and ordering the world, both in science and in society at large. Thus, in this research and in virtually all areas of modern society computers have become indispensable. Pharmacoinformatics is an important branch of information technology in which pharmacology and information systems are merged.

Pharmacoinformatics is one of the latest terms added to the specialized informatics sciences which more or less flourished with the information technology revolution in the 1990's (Rochon, *et al*., 2006). Information technology which uses the computer for data processing and decision making has influenced all kind of sciences. Many of the industrialist and research scientists and academicians are seriously thinking about the need of information technology in pharmaceutical sciences including clinical pharmacy and pharmaceutical care (Spiro, *et al*., 2010). Information technology has been applied indirectly in the drug discovery process and patient care for a long period of time (James, *et al*., 2009).

Pharmacists should be involved in the original conceptual design of some systems that advance information technology to a higher level in Pharmacy Practice. This involvement will enable pharmacists to utilize computer technology to the maximum

level for the purpose of patient care and safety. Pharmaconformatics involves the study, design and implementation of information and information systems in pharmacy.

In the academic setting, Pharmacoinformatics can be better organized such that information for students or members provides a better quality of learning. Educational materials that are indexed, cross-referenced and reviewed properly are easily converted to a database that can be made available via the Web, in a slide-show format, textbooks, or pamphlets. Teaching pharmacy students from the very beginning to adopt technology on a proactive basis can make them more prepared to accept this technology in their future work places like hospitals, community pharmacies and universities.

By improving the computer information systems for the pharmacist, the pharmacy informatics specialist assists other healthcare providers through different ways. First, the pharmacist makes the information more readily available in many shapes and forms which can be utilized by other healthcare professionals. By arranging these systems properly, a comprehensive resource for drug information can be created. Second, pharmacists who spend less time dealing with old standard information systems are now available for their patients, practicing patient counseling, drug monitoring and follow-up. This also gives them ample time to provide training for other healthcare professionals in the institution.

1.2. Aims

The aim of this research is to develop a model for the prediction and calculation of the possible occurrence of ADRs in a specific population. This can be done using certain factors mentioned in medical literature which affect the development of that ADR. The aim of the model is to minimize ADRs and help in choosing the best drug of choice.

This research will generate a concept for creating and utilizing the clinical decision support systems which are the active knowledge systems using two or more items of patient data to generate case-specific - advice.

Clinical characteristics that might be used as predictors of the clinical outcome may include quite diverse features, depending on the particular clinical problem.

The development of this model allows it to be used with any drug. However, for simplicity and to further clarify the concept of this model, antihypertensive drugs were selected.

1.3. Scope of research

Due to the deficiency of the currently available pharmacoinformatic systems, the incidence of ADRs are not satisfactorily prevented (Demiris, *et al*., 2008). This creates an urgent need for a new research approach in this field. It is worth undertaking

research on the use of information technology in ADR predictions. Accordingly, this research will provide a model which enables healthcare professionals to explore and identify the incidence of ADRs for specific drugs. The resulting model should lead to improving pharmacotherapeutic outcomes. This research, therefore, has been structured around four key questions. Firstly, what are the external factors that influence the occurrence of ADRs? To answer this question, certain environmental factors which surround the patient during the treatment period must be studied. Secondly, what are the internal factors (patient related factors) that affect the body making it more vulnerable to ADRs? This question demands the identification of biological and pharmacokinetic differences between patients. Thirdly, what are the expectations and purposes of developing an ADR prediction model? This question requires the assessment of available pharmacoinformatic technology and the actual impact of such technology on patient pharmacotherapeutic outcomes.

Finally, the last question, what are the challenges of implementing such technology in the medical field? This final question will be covered in detail in the final discussion.

1.4. Research objectives

In order to meet the aims of developing an ADR prediction model, the following objectives need to be fulfilled:

1. Develop a mathematical approach for the prediction of ADRs using a selected number of antihypertensive drugs as a basis for the model.

2. Calculate the exact effect of each causative factor on the development of ADRs for a specific drug.

3. Evaluate the validity of the data extracted from literature about the prevalence of ADRs and the possibility of implementing this data on certain populations.

4. Evaluate the effect of poly-pharmacy on the occurrence of ADRs.

5. To evaluate the availability of detailed information about the number and percentage of patients who developed ADRs in medical literature.

1.5. Type of data collection

The primary source of data will be from medical literature. This data will be about the percentage of ADR occurrence in specific patients, considering their specific causative factors and evaluating the effect of these factors on that percentage. The causative factors and their effect on ADR occurrence will be evaluated through medical literature. Also the actual occurrence of ADRs will be evaluated considering these causative factors. These two results will be compared.

Chapter 2

Literature review

2.1. Background

This chapter will discuss the following sections; definition and seriousness of ADRs, the importance of information systems in detecting, reporting and preventing ADRs, factors affecting the occurrence of ADRs and the need for more advanced pharmacoinformatic models for ADR prediction.

2.2. Literature review on ADRs

2.2.1. Definition of ADRs

ADR is defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (WHO, 1972). It is also defined as an undesirable effect, reasonably associated with the use of the drug that may occur as a part of the pharmacological action of a drug or may be unpredictable in its occurrence (Edwards, 2000). Medical literature mentioned many other definitions related to adverse events in addition to ADRs, these definitions are;

1. Unexpected Adverse Reaction is an adverse reaction in which the nature or severity of it is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug (Brennan, *et al*., 2004).

2. Adverse Event / Adverse Experience are any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. This is a more recent term which some use interchangeably with adverse reaction, but, as indicated, it is better reserved for clinical phenomena occurring during drug treatment where the possibility of a causal connection has not been considered (Meyboom, *et al*., 1997).

3. Side Effect is any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug. This is an old term and is broad enough to include both positive and negative effects of a drug apart from its main properties or indications. Some use the term as synonymous with adverse reaction, but the proposed definition will improve clarity of use of this term (Evans, *et al*., 2003).

4. The signal is reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information (Nebeker, 2004). Signal describes the first alert of a problem with a drug. By its nature a signal cannot be regarded as definitive but indicates the need for further enquiry or action. On the other hand it is prudent to avoid a multiplicity of signals based on single case reports since follow up of all such

would be impractical and time consuming. The definition allows for some flexibility in approach to a signal based on the characteristics of individual problems. Some would like a signal to include new information on positive drug effects, but this is outside the scope of a drug safety programme (Veenstra, 2001).

5. Serious adverse event or reaction is any untoward medical occurrence that at any dose:

   - Results in death.
   - Requires inpatient hospitalization or prolongation of existing hospitalization.
   - Results in persistent or significant disability/incapacity.
   - Is life-threatening.

To ensure no confusion or misunderstanding of the difference between the terms serious and severe, the following note of clarification is provided: The term severe is not synonymous with serious. In the English language, severe is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) which is based on patient/event outcome or action criteria serves as guide for defining regulatory reporting obligations (Wooten, 2009).

1. Certain is a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary (Molokhia, *et al*., 2009).

2. Probable/ likely is a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition (Puijenbroek, *et al*., 2001).

3. Possible is a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear (Puijenbroek, *et al*., 2001).

4. Unlikely is a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations (Castel, *et al*., 2003).

5. Conditional/ unclassified is a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination (Naranjo, *et al*., 1981).

6. Unassessible / unclassifiable is a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified (Nebeker, *et al*., 2004).

2.2.2. Classification of ADRs

Gharaibeh, *et al*. (1998) mentioned the following classifications for ADRs severity:

- Mild; No antidote or treatment is required; hospitalization is not prolonged.
- Moderate; A change in treatment (eg, modified dosage, addition of a drug), but not necessarily discontinuation of the drug, is required; hospitalization may be prolonged, or specific treatment may be required.
- Severe; An ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADR. This definition is debatable since severity and seriousness is completely different issues.

2.2.3. Types of ADRs

ADRs are divided into many types depending on the nature, location, causality, and seriousness of the reaction. The types are:

2.2.3.1. Type A Adverse Effects: Drug Actions

Type A effects are adverse effects in the true sense of the word. They are pharmacological actions as much as therapeutic effects are; the essential difference being that they are unintended. Examples are constipation during the use of morphine for analgesia, or sedation caused by a hypnotic. Undoubtedly, type A effects are by far the most prevalent (Trick, 1996). As a rule there is a dose-response relationship: type A effects are more frequent and more severe when higher doses are taken. There is often also a suggestive time relationship between exposure and effect, in accordance with the pharmacokinetic or pharmacodynamic properties of the drug. Because of their pharmacological nature, type A effects are comparatively easy to study.

Clinical trials give information on the efficacy and tolerability; the latter is largely determined by type A adverse effects. In addition, type A effects can often be reproduced and clarified in a variety of experimental tests (e.g. animal experiments or in vitro studies) (Aronson & Ferner, 2003).

Nevertheless, there are many possible reasons why a predominantly pharmacological effect may be less easy to demonstrate and may not be detected in a clinical trial. The

delayed discovery of coughs induced by ACE inhibitors years after their introduction, is an example (Pylypchuk, 1998). A high background frequency or unspecificity of the event may blur the relation with the drug; the mechanism may be unrelated to the therapeutic action of the drug; the effect may only develop after prolonged administration of the drug. In the example of coughs and ACE inhibitors a clear dose response-relationship could not be demonstrated, suggesting the existence of a sensitive subpopulation. A variety of pharmacological (type A) effects occur mainly in special situations or patients with increased susceptibility, for example, demographic determinants, pre-existent disturbances of drug handling, special physiological states, or concomitant use of other medicines or drugs (Aronson & Ferner 2003).

There are many drugs that are generally well tolerated, but exert selective toxic effects on one particular organ, tissue or structure, for instance because of accumulation or the production of toxic metabolic intermediates in the particular tissue. Examples are aminoglycoside and ototoxicity or chloroquine-induced retinopathy ('bull's eye') (Meyboom, *et al*., 2000).

There are many examples of type A effects that take months or even years of drug use to develop (e.g. tardive dyskinesia induced by antipsychotics) (Schooler, *et al*.,1982). Their detection may be difficult because of the absence of a suggestive time relationship.

There are many different physiological or pathological states that predispose to the development of basically pharmacological effects. Pregnancy, lactation, childhood, elderly, decreased renal clearance or haemodialysis, all have characteristic features which may allow medicines to exhibit effects that would otherwise be rare or could not occur (Forfar & Nelson, 1973) . The notorious teratogenicity of thalidomide is a clear example. Because trial patients are selected, clinical trials are unlikely to yield information regarding such special populations (Neubert, *et al*., 1995). Other methods of detection, for example those used for type B adverse effects, may be needed (Aspinall, *et al*., 2002).

Since many drugs may interact in many different ways, drug-drug, drug-food or medicine-drug (e.g. alcohol) interactions play an important role in pharmacovigilance (David, 2000). Because of their pharmacological mechanism, interactions can often be classified as type A effects. Sometimes drugs react physicochemically when exposed outside the body, for example, when injected into an intravenous line (Zwart-van Rijkom, *et al*., 2009).

2.2.3.2. Type B Adverse Effects: Patient Reactions

The second major category, the type B adverse effects, refers to the phenomenon that a drug is well tolerated by the (vast) majority of users, but occasionally elicits an allergic reaction (Rawlins, 1995). Often and characteristically, type B effects are acute, unexpected and severe (Trick, 1996).

Type B adverse effects are a major reason for withdrawal of drug from the market (Aronson1 & Ferner, 2005). Characteristically, there is little or no dose relationship: the reaction is not more frequent or more severe in patients using higher doses. Therefore, type B effects are depicted to be opposite type A effects. Type B adverse effects are either immunological or nonimmunological forms of hypersensitivity and occur in patients with an, often unknown or unrecognised, predisposing condition. Immunoallergic reactions may have complex pathology and take many forms, ranging from nonspecific rashes to specific reactions such as cholestatic hepatitis, agranulocytosis or autoimmune syndromes. Several drugs are known directly that is, without the involvement of an antigen-antibody reaction to release mediators of inflammation (notably histamine) and elicit pseudoallergic reactions, for instance morphine-induced urticaria or aspirin (acetylsalicylic acid)-mediated bronchospasm (Roederer, *et al*., 1991).

The notion of 'intolerance' usually refers to patients with an excessive response to a normal dose of a drug, for example, because of a slow metabolism (Troisi, *et al*., 1985). The response is qualitatively normal but quantitatively excessive.

In the case of idiosyncrasy (a word indicating that the reaction is determined by the constitution of the patient), the response is also qualitatively different (Westphal, *et al*., 1998). Among the many examples are haemolytic reactions in patients with glucose-6-

phosphate dehydrogenase (G6PD) deficiency and, possibly, phenylbutazonerelated aplastic anaemia (Ulrich, 2006). Type B adverse effects are notoriously difficult to study experimentally and often the mechanism is not known or not fully clarified (Dominguez, 2000). There are several examples that a drug was withdrawn because of an idiosyncratic reaction, whereas the underlying mechanisms was never elucidated (a striking example was the practolol-associated sclerosing peritonitis) (Brown, *et al*., 1974).

That type B adverse effects, in spite of so much difficulty, are often readily detected, is explained by the situation that these effects often occur in a suggestive time relationship with drug exposure, are characteristic and have a low background frequency. In this light it is understandable why spontaneous reporting, the major system used by national pharmacovigilance centres, has been found to be especially effective in detecting type B adverse effects (Meyboom, *et al*., 1992).

2.2.3.3. Type C Adverse Effects

Since the controversy regarding increased cardiovascular mortality in patients with diabetes mellitus using oral hypoglycaemic drugs emerging from the prestigious University Diabetes Group Diabetes Program report in the early seventies, numerous connections have been assumed to exist between drug exposure and disease frequency (Garratt, *et al*., 1999). Another example is the increased overall occurrence of malignant diseases observed in clofibrate-users in a large multinational study of the prevention of

ischaemic heart disease (Rosenhamer & Carlson, 1980). Such type C adverse effects can be defined as the increased occurrence of a given disease in patients using a particular drug, as compared with the (relatively high) background frequency in unexposed patients. Compared with type B adverse effects, type C effects have a higher background frequency and a less obvious time relationship (Bankowski, *et al*., 1999). Type C adverse effects, like type B adverse effects, are often difficult to study in experimental models and the mechanism often is unknown (Bankowski, *et al*., 1999).

2.2.3.4. Indirect Adverse Effects

Apart from therapeutic administration, drug can, throughout the process of production, distribution and destruction, give rise to health hazards in a variety of ways. A production error during drug manufacturing could lead to contamination of the environment with a toxic intermediary or waste product. Widely used drugs, that are excreted unchanged or as an active metabolite may be traceable in the surface water. Meyboom, *et al*. (2000) found that antibacterial use in, for instance in bio-industry, may lead to bacterial resistance development.

2.2.4. Magnitude of ADRs

A serious ADR is any untoward medical occurrence that at any dose; results in death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is life-threatening (Aronson, *et al*.,

2003). Serious ADRs are usually preventable, and reducing severe ADRs can be accomplished by strategies targeting the prescribing habits and the monitoring plans and follow-up.

ADRs are one of the leading causes of morbidity and mortality in healthcare. The Institute of Medicine, in the United States (US) (2000) reported that between 44,000 to 98,000 deaths occur annually from medical errors. Of this total, an estimated 7,000 deaths occur due to ADRs. Analyzing 39 studies of the American pharmaceutical system over four decades found that in 1994, 106,000 people died as a result of ADRs. More than 2 million suffered serious side effects (Pomeranz, 1998). These figures showed that there was a trend of increasing death and injury from ADRs during the forty-year range of that particular study. That would make ADRs the fourth leading cause of death in the US behind heart disease, cancer & strokes (Jemal, 2005).

In another survey conducted by the American Society of Health-System Pharmacists, Johnston, *et al*. (2006) found that 85% of patients who responded to the survey expressed concerns about at least one drug-related issue, such as receiving interacting drugs, having harmful adverse effects from a drug, or receiving the wrong drug. ADRs are a significant public health problem in the world. For the 12,261,737 Medicare patients admitted to US hospitals, ADRs were projected to cause the following increases: 2976 deaths, 118,200 patient-days, $516,034,829 in total charges,

$37,611,868 in drug charges, and $9,456,698 in laboratory charges (Bond & Raehl, 2006).

The Institute of Medicine, (2000) reported that there were about 100,000 deaths in the US due to medical errors of which about 7,000 were attributed to drug reactions. Not only do ADRs cause death and injury but they also affect the length of stay in hospitals which in turns lead to increased health care costs and decreased patient's productivity. Moura, *et al*. (2009) determined the frequency of ADRs in intensive care units and to evaluate their effect on the length of stay found out that each ADR presented by the patient was related to an increase of 2.38 days in the ICU.

In research done at the University of Liverpool 18,820 patients were assessed. These were aged older than 16 years and were admitted to two of the national health service (NHS) hospitals in the region over a 6-month period. They found that a total of 1225 admissions were related to an ADR, giving a prevalence of 6.5%. The average stay was 8 days, which accounted for 4% of the hospital bed capacity (Nainggolan, 2004). Lesar, *et al*., (1997) evaluated drug-prescribing errors in a teaching hospital for a 9-year experience of prescription behavior. They showed that a total of 11,186 confirmed drug-prescribing errors with potential for adverse patient consequences were detected and averted during the study period.

Another prospective cohort study was carried out to evaluate more than 1200 outpatient prescriptions, surveyed patients, and conduct a chart review during a 4-week period. The researchers discovered that 25% of patients experienced an ADR with selective serotonin-reuptake inhibitors, beta blockers, angiotensin-converting-enzyme inhibitors, and nonsteroidal anti-inflammatory drug classes the most frequently implicated. The rate of ADRs has approached 27 per 100 patients (Gandhi, *et al*., 2003).

ADR reporting has yet to be developed adequately. The need for increased awareness of the importance of ADR reporting is vital in Malaysia (Aziz & Siang, 2007). It is documented that hospital admissions due to drug and chemical poisoning are not reported separately as a health performance indicator, but are collectively reported with other cases of accidental injury precluding its use to estimate the prevalence of poisoning (Rajasuriar, 2007).

2.3. Factors affecting the occurrence of ADRs

2.3.1. Background

Pirmohamed, *et al*., (1994) suggested that for most adverse reactions, particularly the idiosyncratic drug reactions, predisposition seems to be multifactorial, involving not only defects at multiple gene loci but also environmental factors such as concomitant infection or the use of other drugs for different diseases. The majority of ADRs occur as a result of the extension of the desired pharmacologic effects of a drug, often due to the substantial variability in the pharmacokinetics and pharmacodynamics seen among patients. For instance; drugs with a narrow therapeutic index, such as warfarin and digoxin, are at higher risk for causing ADRs, particularly when toxicity can occur at drug concentrations at or near the upper end of the therapeutic range.

Pharmacological, immunological, and genetic factors are involved in the pathogenesis of ADRs. Factors that predispose to pharmacological ADRs include dose, drug formulation, pharmacokinetic or pharmacodynamic abnormalities, and drug interactions. The metabolic conversion of drugs to chemically reactive products is now established as a requirement for many idiosyncratic drug reactions (Masubuchi, *et al*., 2007). Increased levels of reactive drug metabolites, their impaired detoxification, or decreased cellular defense against reactive drug products appears to be an important initiating factor (Guengerich, *et al*., 2007). Immunological and genetic factors may play a role in the reaction of the body towards the drugs given. Torpet, *et al*. (2004)

suggested ethnic variations also play an important role in the development of ADRs. Further details on each factor will be discussed under each sub title below.

Evans (2005) found that some risk factors are consistent for all ADRs and across multiple therapeutic classes of drugs, while others are class specific. High-risk agents should be closely monitored based on patient characteristics (gender, age, weight, creatinine clearance, number of comorbidities) and drug administration (dosage, administration route, number of concomitant drugs).

Factors which might increase the possibility of the occurrence of ADRs include; extremes of age, gender, multiple drugs, disease state, past history of ADR or allergy, genetic factors, large doses and many other factors as mentioned later in this chapter. Some studies show similarities in the incidence of ADRs between male and female gender even though the majority of deaths involved persons 60 years of age and older (Chyka, 2000). On the other hand; Martin, *et al*. (1998) showed that age and sex differences may contribute in the development of ADRs, In general practice in England for example, suspected ADRs to newly marketed drugs are recorded more often in adults aged between 30 and 59 years of age and are 60% more common in women than in men. The sex difference occurs in all age groups over 19 years of age.