THERAPEUTIC DRUG MONITORING SERVICE IN MALAYSIA: CURRENT PRACTICE AND COST EVALUATION

by

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DEDICATION

To

This thesis is dedicated to my Parents
(Elhag Ahmed and Batool Osman), sisters (Hanadi and Halla)
and brothers (Imad, Haitham and Hani) Their unconditional support of love, encouragement and duaa never seized to lift me during hard times. To my smaller family: my wife Hiba and children; Marwa, Nada and Mohamed who made every single moment worthwhile and where with me every step of the way. I can only say
Allah grant you al-Janna.

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LIST OF ABBREVIATIONS

AFB	Acid fast bacilli
ASHP	American Society of Health-System Pharmacists
BSc	Bachelor of Science
^{0}C	Degree Celsius
CAP	Community acquired pneumonia
CCU	Critical care unit
cm	Centimeter
CME	Continuous Medical Education
CNS	Central nervous system
CPS	Clinical Pharmacokinetic Service
CsA	Cyclosporine-A
CSF	Cerebrospinal fluid
C&S	Culture and sensitivity
D5%	Dextrose 5%
ELISA	Enzyme-Linked Immunosorbent Assay technique
EMIT	Enzyme Multiplied Immunoassay Techniques
FPIA	Fluorescence Polarization Immunoassay
GLC	Gas-Liquid Chromatography
HKL	Hospital Kuala Lumpur
HPLC	High Pressure Liquid Chromatography
HUKM	Hospital Universiti Kebangsaan Malaysia
HUSM	Hospital Universiti Sains Malaysia
IC	Identity card
ICU	Intensive care unit

I.V.	Intravenous route
IU	International unit
Kg	Kilogram
LOS	Length of hospital stay
m	Meter
mg/dl	Milligram per deciliter
μg/ml	Microgram per milliliter
MIC	Minimum inhibitory concentration
mmol/liter	Millimole per liter
μmol/liter	Micromole per liter
MOH	Ministry of Health
MPharm	Master of Clinical Pharmacy
MSc	Master of Science
NS	Normal saline
ORL	Otolaryngology
pH	Measure of the acidity or alkalinity of a solution.
PharmD	Doctor of pharmacy
PhD	Doctor of Philosophy
pKa	The negative log of the acid ionization constant
QA	Quality assurance
QC	Quality control
RCPA	The Royal College of Pathologists of Australia
RIA	Radioimmunoassay
RIQAS	International External Quality Assessment
RM	Ringget Malaysia

RN	Registration number
SPSS	Statistical Package for Social Sciences
TDM	Therapeutic drug monitoring
TFC	Turbulent Flow Chromatography
TR	Therapeutic range
UMMC	Universiti Malaya Medical Centre
UKNEQAS	United Kingdom National External Quality Assessment Service
WBC	White blood cells

PERKHIDMATAN PEMANTAUAN DRUG TERAPEUTIK DI MALAYSIA: PRAKTIS SEMASA DAN PENILAIAN KOS

ABSTRAK

Pemantauan drug terapeutik (TDM) telah dikenalpasti sebagai satu alat klinikal yang berguna dalam terapi drug. Walaupun ia telah bermula sejak tahun 1980an lagi di negara ini, hanya sedikit sahaja kajian yang telah dilakukan mengenainya. Oleh yang demikian, kajian ini bertujuan untuk menilai amalan perkhidmatan TDM di hospital-hospital di Malaysia dan mengenalpasti kos dan hasilan klinikal perkhidmatan ini dalam pesakit yang dimasukkan ke hospital. Kajian ini terdiri dari dua bahagian yang berkait rapat. Bahagian pertama mengenalpasti amalan semasa perkhidmatan TDM dalam hospital-hospital di Malaysia menggunakan borang soal-selidik. Soal-selidik dihantar kepada 128 hospital di Malaysia. Data yang dikumpulkan termasuk ciri-ciri umum hospital, aktiviti-aktiviti pentadbiran, klinikal dan makmal berkaitan perkhidmatan TDM. Dari 121 hospital yang memberikan respon kepada soal-selidik tersebut, 34 hospital (28.1%) memberikan perkhidmatan itu dengan makmal TDM mereka sendiri, 44 hospital (36.4%) menggunakan makmal hospital lain dan 43 hospital (35.5%) tidak memberikan perkhidmatan tersebut. Bahagian kedua kajian ini dijalankan untuk menilai kos menyediakan perkhidmatan TDM di kalangan pesakit yang dimasukkan ke hospital. Penilaian ini dijalankan di dua buah hospital menggunakan kaedah pengumpulan data secara retrospektif. Data dari pesakit dewasa yang dimasukkan ke hospital yang didiagnos bronkopneumonia dan dirawat dengan gentamisin di antara tahun-tahun 2001 hingga 2005 dikaji. Data yang diambil dari Hospital Universiti Sains Malaysia (HUSM) digunakan untuk menentukan kos yang dikaitkan dengan pemberian perkhidmatan TDM tersebut. Data yang dikumpul

dari Hospital Kulim digunakan untuk membandingkan kos dan hasilan antara kumpulan pesakit yang menerima perkhidmatan TDM (Kumpulan TDM) dan kumpulan yang tidak menerima perkhidmatan tersebut (Kumpulan Tiada TDM). Semua kos kemasukan hospital dikira dalam nilai Ringgit Malaysia (RM), termasuklah perkhidmatan TDM, penyiasatan makmal dan klinikal, dos gentamisin, kakitangan wad, dan tempoh tinggal di hospital. Ukuran hasilan termasuk tempoh demam, tempoh tinggal di hospital semasa terapi gentamisin dan kejadian nefrotoksisiti. Data dari HUSM menunjukkan kos perkhidmatan TDM menyumbangkan lebih kurang 23% kepada jumlah kos kemasukan hospital. Di antara kos perkhidmatan TDM, kos alatan makmal adalah yang tertinggi (42%) diikuti dengan kos reagen dan alatan pakai habis (39.7%), pasukan TDM (9.6%) dan ruang makmal (8.6%). Data dari Hospital Kulim menunjukkan kos yang dikaitkan dengan tempoh tinggal di hospital dan jumlah kos kemasukan hospital adalah lebih tinggi dan signifikan dalam Kumpulan TDM berbanding dengan Kumpulan Tiada TDM. Walau bagaimanapun, tidak terdapat perbezaan yang signifikan dalam lain-lain parameter hasilan di antara dua kumpulan tersebut. Sebagai kesimpulannya, kajian ini menunjukkan bahawa perkhidmatan TDM disediakan oleh kebanyakan hospital di negara ini. Data dari HUSM menunjukkan perkhidmatan ini dalam pesakit bronkopneumonia tidak mempengaruhi keseluruhan kos hospital. Data dari Hospital Kulim pula menunjukkan perkhidmatan ini meningkatkan jumlah kos kemasukan ke hospital dengan signifikan dan tidak memberikan impak yang signifikan ke atas hasilan klinikal pesakit.

THERAPEUTIC DRUG MONITORING SERVICE IN MALAYSIA: CURRENT PRACTICE AND COST EVALUATION

ABSTRACT

Therapeutic drug monitoring (TDM) has been recognized as a useful clinical tool in drug therapy. Although it was started in the 1980s in this country, very few studies had been performed to evaluate the service. Therefore, this study aims to evaluate the practice of the TDM service in Malaysian hospitals and to determine the cost and impact on clinical outcomes of providing this service in hospitalized patients. The study consists of two related parts. The first part determined the current TDM practice among government hospitals in Malaysia using a survey questionnaire. Questionnaires were mailed to 128 hospitals in Malaysia. Data were collected for general characteristics of the hospitals, administrative, clinical, and laboratory activities related to TDM service. Out of 121 hospitals which responded to the survey, 34 hospitals (28.1%) provided the service using their own TDM laboratories, 44 hospitals (36.4%) provided the service using other hospitals' laboratories and 43 hospitals (35.5%) did not provide the service at all. The second part of this study was conducted to evaluate the cost and clinical outcomes of providing the TDM service in hospitalized patients. This evaluation was carried out in two hospitals using retrospective data collections. Data from all hospitalized adult patients diagnosed with bronchopneumonia and treated with gentamicin between the years 2001 to 2005 were included. Data collected from Hospital Universiti Sains Malaysia (HUSM) were used to determine the cost of providing the TDM service. Data collected from Hospital Kulim was used to compare the cost and outcome between the group which

was provided with the TDM service (TDM group) with the group which was not provided with the service (Non-TDM group). All hospitalization costs were calculated in Ringgit Malaysia (RM), which included TDM service, laboratory and clinical investigations, gentamicin doses, ward staff, and hospital stay. Outcome measures included duration of fever, length of hospital stay during gentamicin therapy and nephrotoxicity incidence. Data from HUSM show that the cost of TDM service contributed about 23% toward the total hospitalization costs. Among TDM service costs, the cost of laboratory equipments was the highest (42%) followed by reagents and consumables (39.7%), TDM team (9.6%), and laboratory space (8.6%). Data from Hospital Kulim show that the costs of hospital stay and total hospitalization were significantly higher in the TDM group compared to the Non-TDM group. However, there was no significant difference in outcome parameters between the two groups. In conclusion, this study has shown that TDM service is offered by the majority of hospitals in the country. Data from HUSM show that providing TDM service to bronchopneumonia patients did not significantly affect the overall hospital cost. Data from Hospital Kulim show that TDM service significantly increased the total cost of hospitalization and had no significant impact on patients' outcome.

CHAPTER ONE

GENERAL INTRODUCTION

1.0 GENERAL INTRODUCTION

Therapeutic drug monitoring is used in pharmaceutical services to enhance patient care. It was first introduced to the clinical practice in the early 1970s. Since the initiation of this service, different studies evaluating TDM laboratory activities, studying the impact of the service on patient outcome, surrogate endpoints, and pharmacoeconomic evaluations have been done worldwide.

TDM service in Malaysia started in 1984 (Hassan, 1990). After more than 20 years of experience, 73 hospitals are providing the service (Ministry of Health, 2005). Although it started long time ago in Malaysia, very few studies have been performed regarding the service. This study has been performed with two main objectives. First was to identify the current practice of the service in government hospitals in Malaysia. The second objective was to evaluate the cost and benefits of providing the service. The study was divided into two parts to achieve each objective separately.

The first part of the study focused on the general provision of the service; availability, laboratory procedures, and staff activities. It was performed using a survey methodology. The second part evaluated the impact of this service in one of the most monitored drugs in Malaysian hospitals on cost and clinical outcome. This second part was carried out in two different hospitals; one university and one public hospital. Preliminary findings suggested that patients on gentamicin were always provided with TDM service in the university hospital. The cost of providing TDM service was compared to other hospital costs in hospitalized patients with bronchopneumonia. In the public hospital, not all patients on gentamicin were provided with TDM service. In this setting, the benefits (in terms of cost and clinical

outcome) of providing TDM service to hospitalized patients with bronchopneumonia were calculated.

CHAPTER TWO

CURRENT PRACTICE OF THERAPEUTIC DRUG MONITORING SERVICE IN GOVERNMENT HOSPITALS IN MALAYSIA

2.1 INTRODUCTION

2.1.1 Therapeutic Drug Monitoring (TDM) service

2.1.1(a) Principles of TDM

Drug concentration in plasma was first analyzed in the late 1950s and early 1960s. The measurement was initially carried out for the purpose of research rather than for routine clinical service (Pippenger, 1979). Not until when the pharmacological activity of a drug was shown to be related to its concentration, did the concentration measurement were routinely done (Spector, 1988).

Therapeutic drug monitoring (TDM) is based on the assumption that, if there is a relationship between the concentration of a drug in a biological fluid and its effect, then the measurement of the biological fluid drug concentrations may be useful for patient care (Watson, 1997; Potter, 2000; Gross, 2001; Gram, 2001). It is defined as a measurement made in the laboratory, which is applied to a small group of drugs in which there is a direct relationship between serum drug concentration and pharmacological response (Watson, 1997; Schumacher and Barr, 1998).

The range of drug concentrations most commonly associated with optimal effect and an acceptable incidence of toxicity is called the therapeutic range. Pharmacokinetics is a mathematical relationship between a drug dosage regimen and the resulting drug concentrations. Clinical pharmacokinetic is the application of these mathematical principles in conjunction with other measures of clinical observation (Mackichan and Comstock, 1986; Nation and Rayner, 2004a). In practice, therapeutic drug monitoring makes use of the measurement of drug concentration and clinical pharmacokinetics to manage patient drug therapy.

2.1.1(b) Clinical applications of TDM

There are many applications of TDM in clinical setting. TDM is used to evaluate the degree of therapeutic response, provide useful information regarding the appropriateness of drug therapy, evaluate for patient compliance with drug regimen, detect suspected adverse effects, and to confirm drug toxicity (Shirrell, 1999; Gross, 2001; Pippenger, 2006). It is also useful in confirming drug interactions, diagnosis of overdosed patients, and mainly dosage adjustment (Spector *et al.,* 1988).

Very old and very young patients and patients with abnormal organ functions, such as renal or hepatic impairments exhibit variation in drug pharmacokinetics. Because of these wide variabilities, TDM is a useful tool in dosage individualization in these patients (Walson, 1998).

In general, patients that may need to be monitored by TDM service include patients with the following characteristics and conditions; renal impairment, hepatic impairment, history of hematological abnormalities, marked cardiac dysfunction, severe airway disease, diabetes mellitus, obstetric problem, on dialysis, elderly patients, children and neonates, obese and malnourished, and burn patients. Those patients who receive drugs that have narrow therapeutic index, high incidence of adverse effects, high incidence of drug interactions, drugs that may induce reactions or hypersensitivity, or newly marketed drugs can also be included (Malaysian Ministry of Health, 2001).

2.1.1(c) TDM process

The TDM team includes clinical pharmacologists, clinical pharmacists and analytical scientists as well as other personnel who participate in patient care such as doctors and nurses (Gross, 2001; Shenfield, 2001). Doctors usually request TDM tests for specific patients according to some specific indications. The nurse is responsible for collecting the blood samples for analysis. Performing the TDM tests is mainly a responsibility of the analytical scientist or technician who is well trained and qualified for this process. After performing the tests and obtaining the results, the clinical pharmacologist or pharmacist interprets these results and converts them into useful information and recommendations to the requested doctor (Koren *et al.,* 1985; Gross, 2001).

Figure 2.1.1 shows a TDM process adapted from Barr and Schumacher (1995). The TDM process consists of four main components that begins and ends with patient care; pre-analytical, analytical, post-analytical, and the regulatory environment. Regulatory environment is the condition and atmosphere that surrounds the analytical procedure. The pre-analytical component consists of 4 steps; the first step starts with the clinical question that arises when the clinician comes across the patient. In the next step, the clinician chooses the test(s) that might answer this question. The clinician orders the test in the third step. At the end of this component, the sample is taken and sent to the clinical laboratory for analysis.

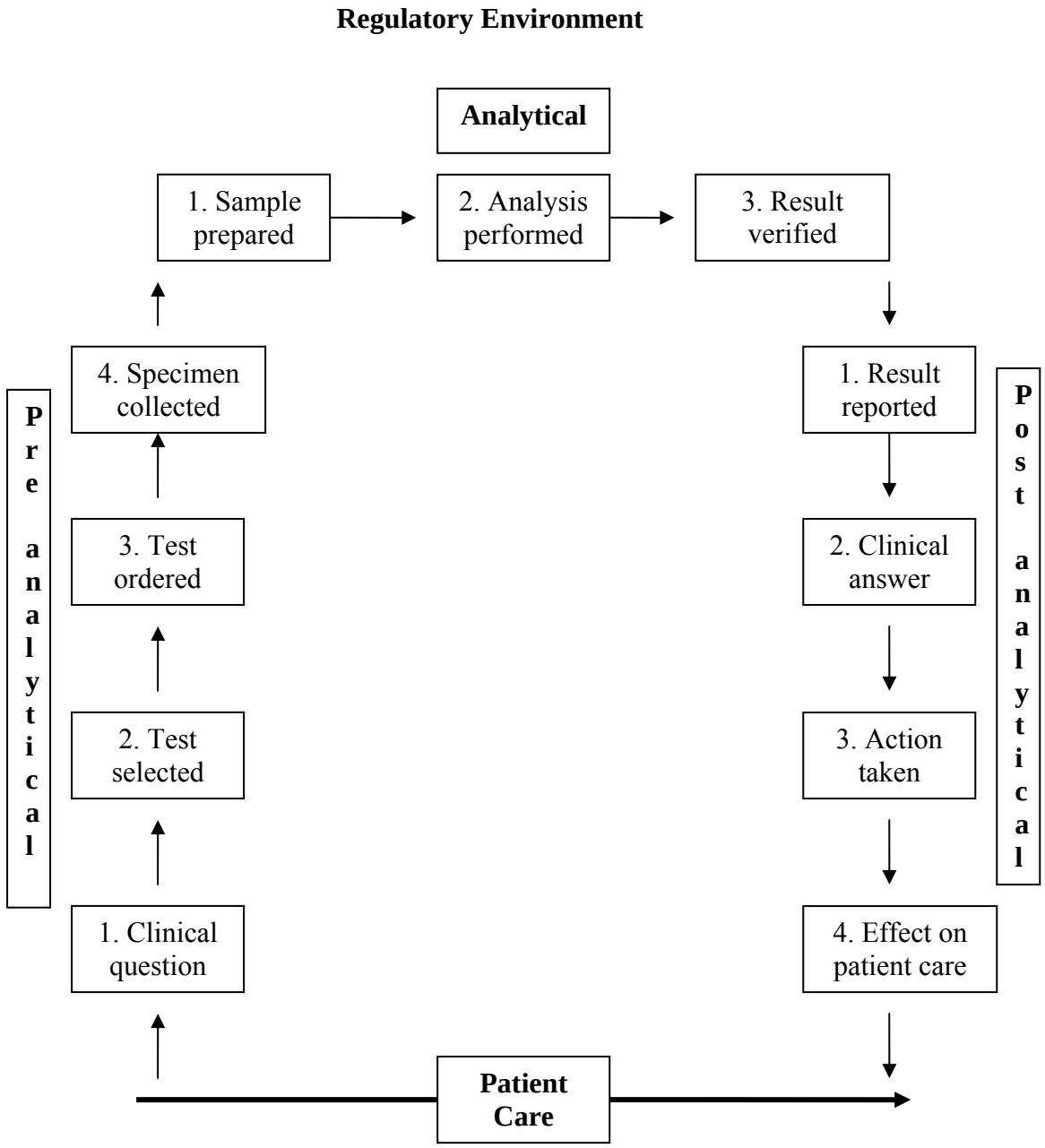

Figure 2.1.1 TDM process (adapted from Barr and Schumacher, 1995)

The second component, which is the analytical component, consists of three steps. The first step is the sample preparation, which consists of transporting the sample to the analysis site and separation of serum or plasma from cellular blood to prepare it for analysis. The second step is performing the analysis using an appropriate assay technique. The third step in this component is to verify the drug analysis result.

The third component has four steps. The first step is reporting the result by either hard or soft copy or both. In the second step, this result is expected to give an answer for the previous clinical question raised in the first component. In the last two steps of this component, the clinician can take action accordingly to meet the patient care needs.

2.1.1(d) Sample matrices

Usually drugs are monitored in venous blood, serum or plasma. Whole blood may be used for some drugs like cyclosporine, tacrolimus, sirolimus, and everolimus which distribute between erythrocytes and plasma (Gross, 2001; Dasgupta, 2008). Saliva can be used instead of blood in case of infants and children (Zalzstein *et al.,* 2003*).* In addition, saliva can be used in the elderly and pregnant women and sometimes in adult patients when venipuncture is difficult. It can be easily collected and preferred by the medical staff as it minimizes their contact to blood samples **(**Barr and Schumacher, 1995**).** Drugs that can be monitored using saliva are phenytoin, carbamazepine, theophylline, digoxin, and lithium. In addition, drugs of abuse such as morphine and cocaine can also be monitored by saliva (Pichini, 1996).

Using urine as a biological matrix for drug monitoring has many advantages. Urine samples can be easily collected and are well accepted by patients. Moreover, urine is preferred because its window for identifying drug use is broader compared to blood. The use of urine in TDM service is applicable to anticonvulsant and psychoactive drugs (Elmquist, 1991; Wu, 1998).

There are some other biological matrices that can be used but to a lesser extent such as tears, which can easily be collected. It seems to be more homogenous and more constant in their composition than saliva. Due to its pH, only unionized and acidic drugs with high pKa values distribute in tears in a predictable manner, which limits its use to small variety of drugs like valproic acid (Pichini, 1996; Nakajima *et al.,* 2000).

Hair as a biological matrix can keep drugs and metabolites indefinitely, in contrast to serum or urine in which drug concentrations decrease rapidly with time. Therefore, hair can be used for forensic purposes as well as in drugs of abuse. Hair testing has some drawbacks due to the difficulty in producing reference material for laboratory practices and to the differences in hair characteristics from one patient to another. Similar to hair, nails are used in drug abuse and forensic examination. Moreover, they can be used in antifungal drugs monitoring. Recently, sweat is being used for determination of drugs of abuse although sampling procedure and method of analysis are very complicated (Pichini, 1996; Palmeri *et al.,* 2000; Pragst and Balikova, 2006). Moreover, sweat is another biological matrix that can be used in forensic examination for detection of drugs of abuse. It can be used in nonvolatile drugs like heroin. The sampling procedure is an easy process, which applied by using sweat patches. It is a noninvasive procedure, requires minimal handling by the operator and is acceptable by patients (Fucci and Giovanni, 2007).

Many studies that are conducted for bile measurement were carried out for patients who have previously undergone biliary tract surgery. Penicillins, cephalosporins, aminoglycosides, and cardiac glycosides are some drugs that have been determined

using bile analysis. Feces are limited to studies in new drug development and may provide information on excretion of drugs and metabolites through its route of excretion (Pichini, 1996).

Fetus blood and amniotic fluid can be used for detecting of drugs that can affect the fetus such as some antibiotics, anticonvulsants and tranquillizers. Additionally, the importance of drug investigation in breast milk is to determine the amount of drug that can be ingested by the breastfeeding infant. Phenobarbital, theophylline, and some psychoactive drugs as well as drugs of abuse might be detected in breast milk (Pichini, 1996; Loebstein and Koren, 2002; Moretti *et al., 2003*).

Drug measurement in cerebrospinal fluid (CSF) is necessary to establish if the concentration of a drug in the central nervous system (CNS) is desirable for the drug effect or not. Collection of CSF is not an easy technique since it is done by lumbar puncture. Examples of drugs that are monitored by CSF measurement are antibiotics that are used in CNS infections, anticonvulsants, psychoactive drugs, and protease inhibitors (Pichini, 1996; Aarnoutse *et al.*, 2001).

Monitoring of drugs in bronchial secretions and peritoneal fluid are rarely used. They are used for patients with serious diseases and require invasive techniques for sample collection. Using interstitial fluid as a biological matrix in neonates may provide information regarding the toxic agents that may be absorbed through the skin. It can be used for analgesics and theophylline that may be applied transdermally. Drug concentration monitoring in cervical mucus is mainly carried out for pharmacotoxicological purposes. For example, it is used to detect the presence of

nicotine and its metabolite in the cervix due to its risk of cervical neoplasia. Examining the seminal fluid is used to determine the presence and concentrations of some drugs that may affect the physiology or activity of semen in man as well as the pharmacological and adverse drug reaction in women exposed to drugs excreted in semen. Drugs like antimicrobials, sulfasalazine, salicylate, propranolol, and protease inhibitors are monitored in the seminal fluid (Pichini, 1996; Aarnoutse *et al.,* 2001).

2.1.1(e) Analytical techniques used in TDM

In the late 1950s and early 1960s, Ultraviolet Spectrophotometry was the first method applied for the analysis of drug concentration in the plasma but it has some disadvantages. It required large volume samples as well as extraction techniques were time consuming and complex. It is considered as the most used technique for the determination of methotrexate (Pippenger, 1979; Rubino, 2001).

In the middle of 1960s, Gas-Liquid Chromatography (GLC) was introduced as a method of separating classes of drugs rapidly and quantitatively at the same time but its main disadvantage was the complexity of its instrumentation. In 1970s, GLC was performed routinely in clinical chemistry laboratories and it is used to measure the concentrations of some antidepressant drugs (Pippenger, 1979; Lacassie *et al.,* 2000).

Radioimmunoassay (RIA) technique was the first immunoassay technique that is used in drug monitoring. It has an advantage that it can measure drug concentration in microvolumes. It has some disadvantages of complexity of its instrumentation as well as time consuming procedure, disposal of radioactive waste, and short shelf-life

of its reagents. It can be used to detect digoxin (Pippenger, 1979; Barr and Schumacher, 1995).

An automated, homogeneous Enzyme Immunoassay Techniques (EMIT) was available in 1970s which enables TDM service to be available to all laboratories. However, it is limited to those drugs for which antibodies are available. It uses a simple technology and has rapid turnaround time with a high accuracy rate. Enzyme-Linked Immunosorbent Assay technique (ELISA) has almost the same technique as other enzyme immunoassays. Separation steps are required for completing the analytical procedure and that is why ELISA is called a heterogeneous method. Besides, it is limited to those drugs that antibodies are available (Pippenger, 1979; Sym *et al.,* 2001).

High Pressure Liquid Chromatography (HPLC) solves a lot of problems regarding the assay of multiple drugs and their metabolites within the same class. It can be applied for many drugs but it has the disadvantages associated with the high turnaround time and that highly skilled personnel are needed to perform the procedures (Pippenger, 1979; Barr and Schumacher, 1995; Jebabli *et al.,* 2007). However, it is used to some extent in teaching hospitals and for research purposes (Gogtay *et al.,* 1999). In the late 1990s, Turbulent Flow Chromatography (TFC) a new chromatographic technique was introduced. It is a fully automated and simple technique. It requires short time for sample preparation and analysis. Mainly it is used for monitoring antidepressant drugs and their metabolites (Sauvage *et al.,* 2006).

Fluorescence Polarization Immunoassay (FPIA) is now the most widely used technique worldwide. It is easy to perform, does not need highly skilled personnel and has shorter turnaround time. Like other immunoassay techniques, measuring serum drug concentration is based on an antigen-antibody reaction. FPIA technique has some drawbacks such as in some drugs like cyclosporine, where metabolites interfere with the reagents' antibodies; and the high cost of its reagents used in the drug analysis (Lee *et al.,* 1991; Morris, 1994; Barr and Schumacher, 1995; Sym *et al.,* 2001). Other techniques that are rarely used in TDM service include Flame emission/absorption methods. These method are used to measure the concentration of drugs like lithium (Thomson *et al.,* 1998).

2.1.1(f) Drugs monitored and sampling time

Drugs monitored by TDM service share some characteristics either they have relatively narrow therapeutic range (TR), or a conventional dose response relationship is deficient (Cuddy, 2000). Others have pharmacological action that is difficult to be measured clinically (McInnes, 1989). Wolf (1996) has proposed the criteria for drugs that should be monitored by TDM service. They include drugs with dangerous toxicity, have narrow therapeutic range, are used in long term therapy, are used in life threatening disease, have interindividual pharmacokinetic variability, drugs with nonlinear pharmacokinetics, drugs with wide distribution in the body, and the availability of reliable analytical techniques to measure the drug's concentration.

Ideally, the drug should be monitored only when it reaches steady state. However, plasma concentration can be measured before steady state in some cases, but still sampling time should be taken into consideration. Sampling time varies with different drugs. To optimize the drug concentration values, blood samples should be

taken at specific times with respect to the last dose taken. Usually drugs are measured just before the last dose (trough level). Aminoglycosides and vancomycin are measured at the trough level and the peak (after giving the last dose) level (Aronson and Hardman, 1993b).

Aminoglycosides like gentamicin (TR peak = 4-8 µg/ml, TR trough = 1-2 µg/ml), amikacin (TR peak = 15-25 µg/ml, TR trough < 5 µg/ml), and tobramycin (TR peak = 4-8 µg/ml, TR trough =1-2 µg/ml), have the same characteristics and they all have a narrow therapeutic index. Moreover, their mechanism of action depends directly on the peak drug concentration in the serum, while the ototoxicity and nephrotoxicity are related mainly to the total amount of drug given. TDM may be useful in keeping the aminoglycosides within the therapeutic range while avoiding toxicity (Triggs and Charles, 1999; Dasgupta, 2008). If the drug is given by IV infusion, the sample should be taken after 15 minutes at the end of the infusion for post-therapy measurement. In case of pre-therapy measurement the sample should be taken just before the next dose. In patients with normal renal function, gentamicin concentration measurement should be carried out within the first 24 hours of treatment to optimize drug therapy (Aronson and Reynolds, 1993a).

Vancomycin (TR peak = 30-40 µg/ml, TR trough = 5-15) has almost the same side effects as aminoglycosides. But it has a different mechanism of action with a so called time-dependent killing, which works better when its trough concentration in the site of infection is higher than the minimum inhibitory concentration (MIC) of the infected organism. Its concentration-independent mechanism has raised considerable arguments regarding the benefits of measuring the vancomycin

concentration. However, not all patients with vancomycin require concentration monitoring. The peak level of vancomycin should be taken within half to one hour after completing the one hour infusion to allow the completion of the distribution phase (Begg *et al.,* 1999; Bauer, 2001; Dasgupta, 2008).

Anticonvulsants like phenytoin (TR= 10-20 µg/ml), phenobarbital (TR= 15-40 µg/ml), valproic acid (TR= 50-100 µg/ml), ethosuximide (TR= 40-75 µg/ml), and carbamazepine (TR= 4-12 µg/ml), are generally monitored in plasma or serum because the concentrations are identical in these two biological matrices (Eadie, 2001; Dasgupta, 2008). Phenytoin lacks a predictable dose-response relationship, and serum drug concentration measurement has proved to be a better indicator of clinical response (Cuddy, 2000). The concentration of phenytoin should be measured after a few days of starting the treatment but practically, the concentration is measured after three to four weeks of continuous dosing (Aronson *et al.,* 1993a). Other drugs also should be monitored when they reach steady states. For example, phenobarbital is monitored after 3-4 weeks, carbamazepine after 2-3 weeks and valproic acid on the second day. However, patients should be monitored in case of worsening of epilepsy or when they have signs of drug toxicity (Bauer, 2001).

Theophylline (TR= 10-20 µg/ml) shares the same criteria of lacking a predictable dose response relationship. Theophylline concentrations may provide diagnostic and predictive information about therapy in overdose cases (Cuddy, 2000; Dawson and Whyte, 2001; Dasgupta, 2008). In case of IV infusion, the sample should be taken after 4-6 hours of infusion; the infusion should be stopped for 15 minutes before taking the sample (Aronson *et al.,* 1993b).

Monitoring of digoxin (TR= 0.8-2.0 ng/ml) can be useful in controlling the therapeutic or toxic effect. Steady state of digoxin can be reached, in case of normal renal function, after eight days of treatment. Digoxin sampling may be carried out at least six hours after the last dose or just before the next dose (Cuddy, 2000; Aronson and Hardman, 1993a; Dasgupta, 2008).

The narrow therapeutic ratio along with the variation in the pharmacokinetics of immunosuppressant drugs such as cyclosporine (TR= 100-400 ng/ml), tacrolimus (TR= 5-15 ng/ml), sirolimus (TR= 4-20 ng/ml), everolimus (TR= 5-15 ng/ml), and mycophenolic acid (TR= 1-3.5 µg/ml) from one person to another highlighted the importance of individualizing the drug therapy using TDM service. TDM service is useful to avoid the rejection of the transplant organ in case of the subtherapeutic levels and to prevent the toxic effects of the drug in case of drug overdose. Cyclosporine sample should be taken before the next dose (Reynolds and Aronson, 1993; Dasgupta, 2008).

Lithium (TR= 0.8-1.2 µEq/l) has a narrow therapeutic ratio and its pharmacokinetics vary from one patient to another. This makes it difficult to accurately predict the dosage regimen of this drug. Lithium samples should be taken after 12 hours from the last dose (Aronson and Reynolds, 1993b; Dasgupta, 2008).

Because of their potential toxicities, serum concentration of drugs like salicylates, ethanol and paracetamol are monitored in some hospitals in all patients who are presented with mental problem (Wu, 1998). Paracetamol should be monitored in all patients who ingested large amount or unsafe dose of the drug. Due to high

variability in its pharmacokinetics and metabolic profile in children and neonates, paracetamol should be monitored to avoid the subtherapeutic and toxic concentrations. Paracetamol sample should be taken at least 4 hours after ingestion of the drug (Dawson and Whyte, 2001; Oliveira *et al.,* 2002).

Other drugs that are also monitored by TDM service include amiodarone (TR= 1-2.5 µg/ml), quinidine (TR= 2-5 µg/ml), procainamide (TR= 4-10 µg/ml), and lidocaine (TR= 1.5-5 µg/ml), methotrexate (TR> 0.01 µicromol), caffeine (TR= 5-15 µg/ml), disopyramide (TR= 1.5-5 µg/ml), and some antituberculin drugs (Gogtay *et al.,* 1999; Baylor, 2007; Dasgupta, 2008).

2.1.2 Literature review of TDM service

TDM service is a widely used clinical service all over the world. However, among hospitals and institutions which provide this service there are variations in the availability, number and source of samples, analytical and clinical activities, participation in quality assurance programs, and educational programs offered.

2.1.2(a) TDM service in developed countries

In Australia TDM service was started in the late 1970s and the early 1980s (Shenfield, 2001). Although TDM service started a long time ago, there are still many hospitals that do not provide this service while others provide it partially with the assistance of other institutions. However, until the late 1990s, about 75% of hospitals in Australia provided TDM service. About 65% of these hospitals perform drug assay measurements in their own laboratories (Morris, 1998). A survey performed by Morris (1994) looking at cyclosporine-A (CsA) monitoring, reported that 93% of TDM laboratories in Australia perform more than 500 CsA tests annually; 10% of these tests were received from external sources rather than the unit that offer the analysis. Most of these laboratories were not included in external quality assurance programs. They use different types of reporting procedures included phone calls, online computer system, and face-to-face communications (Morris, 1994). The number of cyclosporine-A samples that monitored in these laboratories increased up to 12770 samples in the year 2000, while the number of laboratories that registered in the International Proficiency Testing Scheme increased to 71% (Morris and Lam, 2002).

In Spain, TDM service was started in 1980. The majority of TDM units in the country began their services in the biochemistry department. The biochemistry department provides the results while the central pharmacology unit in the hospital provides the recommendations to the doctors. Vall d'Hebron is a public institution that covers four main hospitals and receives samples from other outpatient clinics with an average of 8800 tests performed in 1990. The service is available for 12 hours daily, Mondays through Fridays except for emergency and some specific cases that had to be performed during weekends. Drugs monitored by the TDM service are anticonvulsants, aminoglycosides, vancomycin, theophylline, and cyclosporine (Pou and Campos, 1992).

In the Netherlands, TDM service started in the early 1980s. It is performed mainly by the hospital pharmacist and it is a part of the pharmacy department in hospitals. Vinks *et al.* (1992) reported that in The Hague Hospitals Central Pharmacy incorporated many different pharmaceutical services including TDM service. This centre performs the TDM service for all participating local hospitals in the area for an average of 12000 samples carried out each year. The service is available seven days a week and operates 24 hours daily. The most common drugs monitored are aminoglycosides and theophylline (Vinks *et al.,* 1992).

Murphy *et al.* (1996) reported that the TDM service first started in USA in the 1970s. TDM service was available during the daily working hours, Mondays to Fridays in most hospitals. Twenty four hours-a-day services and on-call services were available in a few hospitals only. Aminoglycosides, vancomycin, theophylline, and cyclosporine, digoxin, antiepileptic drugs, lithium, methotrexate, caffeine,

ethosuximide, warfarin, and procainamide are the common drugs monitored by the TDM service. TDM pharmacists participated in continuous educational programs to increase their skills and competence (Murphy *et al.,* 1996).

In the state of Georgia, TDM service was available in 23.3% of hospitals. TDM laboratory was a part of the pharmacy department in 93% of the hospitals. Drugs monitored were aminoglycosides, vancomycin, theophylline, cyclosporine, digoxin, antiepileptic drugs, lithium, methotrexate, warfarin, and procainamide. An average of 1000 samples was performed annually in some hospitals (Murphy *et al.,* 1991).

Howard *et al.* (1994) found that 70% of all veterans affairs medical centre in USA provided TDM service. The majority (82%) of hospitals started providing the service within the last nine years before this survey. However, more than half (68%) of hospitals in veterans affairs started providing the service since 1990. In a recent national survey, Pedersen *et al.* (2000) reported that 75% of hospitals in USA provide TDM service for inpatients. The pharmacists in these hospitals routinely provided recommendations for adjusting and calculating the dosage for those drugs that are monitored in their hospitals.

In Japan, TDM service started in Kyushu University Hospital in 1981. The pharmacy department provides the service within their own TDM laboratory which is located in the hospital. An average of 4350 requests was performed annually in the unit. The sources of these samples were mainly from inpatient and outpatient clinics. Antiepileptics, aminoglycosides, theophylline, digitals, lithium, methotrexate, and disopyramide were the most common drugs monitored by the unit (Ieiri *et al.,* 1990).

In Canada, TDM service started in the Hospital of Sick Children in 1981. The TDM laboratory was managed by a clinical pharmacist of the clinical pharmacology division. The service was available seven days a week, 24 hours a day. Thirteen different drugs (antibiotics, cardiovascular drugs, anticonvulsants, theophylline, and methotrexate) were monitored daily in the hospital, with an average of 19200 samples performed yearly. It was found that the service had an impact of decreasing the toxic level of drugs monitored (Koren, 1985).

A survey of 157 TDM laboratories, mainly from Europe, Asian and African countries found that different reporting procedures were used in these laboratories. They ranged from producing hard copy reports, phone calls, and fax, to using online computer reporting. Some of these laboratories reported that insufficient information in the TDM request form was the main problem faced by the TDM service (Thomson *et al.,* 1998).

2.1.2(b) TDM service in developing countries

In Iran, TDM service first started in 1984 at the Tehran University of Medical Sciences Hospital. Drug samples were analyzed at their own TDM laboratory, which was located in the hospital. Samples were received from their own hospital departments as well as from other clinics and neighboring hospitals. Phenobarbital and phenytoin were the first drugs monitored by the TDM unit. Many other drugs were included later on to be monitored by the service (Bigdeli, 1992).

TDM service was started first in Turkey in the late 1980s by the Pharmacology department in Istanbul Medical Faculty Hospital. Eighty-four percent of the samples

came from their hospital departments and 16% came from other hospitals. More than 5500 tests were monitored annually by the TDM unit. Drugs monitored were antiepileptics, digoxin, theophylline, and salicylates (Yamantürk *et al.*, 2000).

In South Africa, Cridland (1994) reported that TDM service was performed mainly by the pharmacology and biochemistry departments of the Groote Schuur Hospital (1470 beds). They performed about 20,300 samples annually. Seventy percent of these samples came from the hospital departments while the rest came from other medical institutions. Common drugs monitored by the hospital included theophylline, digoxin, antiepileptics, and cyclosporine.

In developing countries like Saudi Arabia and Egypt, evaluation of TDM service has been performed. Desoky *et al.* (2003) evaluated the impact of TDM service on the distribution of the drug concentrations. They found no differences in the rates of subtherapeutic, therapeutic or toxic drug levels for digoxin, carbamazepine, phenytoin, and valproic acid between the two countries.

2.1.2(c) TDM service in Malaysia

Malaysia is located in South East Asia with an area of 329,750 square kilometer. It has a population of 23,953,136 (Information Centre Malaysia, 2005). The first TDM service in Malaysia was offered by the School of Pharmaceutical Sciences in the Hospital Universiti Sains Malaysia (HUSM) in the year 1984 (Hassan, 1993). Gentamicin was the first drug monitored by TDM service in HUSM (Ismail, 1990). Commonly monitored drugs in HUSM were paracetamol, aspirin, theophylline,

aminoglycosides, vancomycin, antiepileptic drugs, digoxin, chloroquine, mefloquine, and procainamide (Hassan, 1990).

In 1987, only four hospitals provided the TDM service. The number of hospitals that provided the service increased to 9, 20, 61, and 73 in the years 1988, 1992, 2002, and 2005 respectively. Fourteen drugs are regularly monitored in government hospitals, which include aminoglycosides, antiepileptics, digoxin, theophylline, cyclosporine, methotrexate, tacroloimus, vancomycin, and lithium. The total number of cases monitored increased from 25,756 in 1998 to 61,907 in 2005 (Ministry of Health, 1988, 1992, 2002a, 2005a).