Seth Kwabena Amponsah
Yashwant V. Pathak *Editors*

Recent Advances in Therapeutic Drug Monitoring and Clinical Toxicology

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I dedicate this book to my mother, Comfort Aboagye-Adu, who through her tireless efforts saw me through my education. Also to my wife, Twumwaa, and children, Ethan and Elsye, who continuously encourage me. I also dedicate this book to my sister, Adwoa, for all her support.

I cannot forget, Prof. George Obeng Adjei, Prof. Jorgen Kurtzhals, and Prof. Kwasi Agyei Bugyei, who have been my academic mentors.

—Seth Kwabena Amponsah

To the loving memories of my parents and Dr. Keshav Baliram Hedgewar, who gave proper direction to my life, to my beloved wife Seema who gave positive meaning, and my son Sarvadaman who gave a golden lining to my life.

I would like to dedicate this book to the loving memories of Ma Chamanlaljee, Ma Lakshmanraojee Bhide, and Ma Madhujee Limaye, who mentored me selflessly and helped me to become a good and socially useful human being.

—Yashwant V. Pathak

Foreword

Over the years, there has been growing interest in the fields of therapeutic drug monitoring and clinical toxicology. However, there appears to be few books that address recent trends. The current book, which I am very glad to write a foreword, has an excellent compilation of information on clinical toxicology and therapeutic drug monitoring.

Due to the fact that medicine is a fast-evolving field, it is important that information on current trends is documented. This book offers thorough, but succinct, details on drug monitoring and clinical toxicology. The book includes dedicated chapters for key topics, including analytical techniques in therapeutic drug monitoring and clinical toxicology, the role of artificial intelligence in therapeutic drug monitoring and clinical toxicity, and analysing data from therapeutic drug monitoring, pharmacokinetics and clinical toxicological studies. I am very confident that this book will be very beneficial to researchers, toxicologists, clinicians and students in the field of biomedicine and clinical sciences. The book contains 21 chapters with rich content, presenting fundamental facts, as well as practical and clinically related data, and ends with challenges and future directions of therapeutic drug monitoring and clinical toxicology. Each chapter is well written, clear, precise and easy to understand. The text integration is a bonus, making it appropriate for all in the sciences.

As a biomedical scientist, I strongly recommend this book to all researchers and students. I consider this book as essential for any reference library. My heartiest congratulations to Seth Kwabena Amponsah and Yashwant V. Pathak for such a laudable initiative. I would definitely have this book on my desk.

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Preface

The correlation between drug concentration in body fluids and outcome is stronger than between drug dose and outcome. Hence, measuring systemic drug concentration is an essential part of therapeutic drug monitoring (TDM). Aside its role in therapy, TDM can also prevent unnecessary therapeutic interventions and subsequently reduce healthcare costs. There is no doubt that recent advances in TDM will shape clinical practice.

Toxicology is multidisciplinary, hence, contributions by diverse scientists. In the modern era, toxicologists share scientific knowledge to obtain accurate data about unwanted effects of different agents. Over the years, advanced tools used in toxicological and epidemiological research have been discovered.

This book gives an overview of TDM and its clinical application (analytical techniques, pharmacokinetic models, etc.). The book also highlights recent advances in toxicological studies.

Furthermore, this book focuses on major aspects of emerging and recent advances in TDM and clinical toxicology. The highlights include

(i) Analytical techniques in TDM and clinical toxicology
(ii) TDM and pharmacokinetic studies
(iii) TDM of drugs with narrow therapeutic indices
(iv) Artificial intelligence in TDM and clinical toxicology
(v) Future directions and challenges

The editors hope that this book will provide current information on TDM and clinical toxicology to healthcare professionals and academicians who work in the field of pharmacokinetics, toxicology, and pharmaceutical chemistry. Additionally, this book will affordably provide information on TDM and clinical toxicology to those interested in drug safety and the need for individualized therapy. The editors envisage that this book will be more of a reference and resource for all stakeholders in the health sciences.

The editors thank all contributing authors, who continue to play critical roles in the field of TDM and clinical toxicology. The editors also thank Springer Nature, for accepting to get this book published.

Accra, Ghana — Seth Kwabena Amponsah
Tampa, FL, USA — Yashwant V. Pathak

Contents

1 Therapeutic and Toxic Concentrations of Drugs in Biological Matrices 1
Seth Kwabena Amponsah and Yashwant V. Pathak

2 Analytical Techniques for Therapeutic Drug Monitoring and Clinical Toxicology 9
Samuel O. Bekoe, Samuel Asare-Nkansah, and Kwabena F. M. Opuni

3 Plasma Therapeutic Drug Monitoring and Clinical Toxicology 21
Gregory Fishberger, Nicole Natarelli, Dao Le, Deborah Liaw, Afrin Naz, Caroline Ward, Michael Young, and Charles Preuss

4 Dried Blood Spots in Therapeutic Drug Monitoring and Toxicology 43
Raphael N. Alolga, Qun Liu, and Qi Lian-Wen

5 The Role of Artificial Intelligence in Therapeutic Drug Monitoring and Clinical Toxicity 67
Surovi Saikia, Jinga B. Prajapati, Bhupendra G. Prajapati, Vijaya V. Padma, and Yashwant V. Pathak

6 Therapeutic Drug Monitoring and Optimal Pharmacotherapy with Medicines of Narrow Therapeutic Index 87
Anthony Kwaw, Arnold Forkuo Donkor, and Kwame Ohene Buabeng

7 Therapeutic Drug Monitoring (TDM) and Toxicological Studies in Alternative Biological Matrices 95
Biswajit Basu, Bhupendra G. Prajapati, Swarupananda Mukherjee, Tapas Kumar Roy, Arnab Roy, Chowdhury Mobaswar Hossain, Jigna B. Prajapati, and Jayvadan Patel

8 Analyzing Data from Therapeutic Drug Monitoring, Pharmacokinetics, and Clinical Toxicology Studies 117
Abdul Malik Sulley

9 Reducing Toxicity in Critically Ill Patients by Using Therapeutic Drug Monitoring 143
Zalak Panchal, Khushboo Faldu, and Jigna Shah

10 Quality Assurance of Samples for Therapeutic Drug Monitoring and Clinical Toxicology 161
Samuel O. Bekoe, Samuel Asare-Nkansah, and Kwabena F. M. Opuni

11 Therapeutic Drug Monitoring and Toxicology of Anticancer Drugs 165
Seema Kohli and Lavakesh Kumar Omray

12 Therapeutic Drug Monitoring and Toxicology of Immunosuppressant 181
Anshul Shakya, Rajdeep Sarma, Neha Ghimire, Surajit Kumar Ghosh, Hans Raj Bhat, and Obaidur Rahman

13 Therapeutic Drug Monitoring and Toxicology: Relevance of Measuring Metabolites 197
James Akingbasote, Sandra Szlapinski, Elora Hilmas, Patrik Miller, and Natalie Rine

14 Recent Advances in Nanosensors for Therapeutic Drug Monitoring (TDM) 233
Percy Selasi Agogo-Mawuli and David P. Siderovski

15 Organ Toxicity by Immunosuppressive Drugs in Solid Organ Transplantation 255
George J. Dugbartey and Alp Sener

16 Artificial Intelligence-Based Techniques to Assess Drug Toxicity in Drug-Induced Liver Injury (DILI) Disease 273
Munish Puri

17 Drug Dose and Therapy Individualization 285
Ashley Mason, Gavin Lockard, Vance Cantrell, Snow Pinxue Li, Kirtan Patel, Sierra Klein, Andre Elder, Melissa Sur, and Charles Preuss

18 Models for Drug Individualization: Patient to Population Level 303
Sierra Klein, Ashley Mason, Gavin Lockard, Vance Cantrell, Snow Pinxue Li, Kirtan Patel, Andre Elder, Melissa Sur, and Charles Preuss

19 Toxicity Evaluation of Nanomedicine 323
Archna Panghal and Swaran Jeet Singh Flora

20 Biochemical Indices of Drug Toxicity 347
Emmanuel Kwaku Ofori

21 Therapeutic Drug Monitoring and Clinical Toxicology: Challenges and Future Directions 369
Seth Kwabena Amponsah and Yashwant V. Pathak

Index 379

About the Editors

Seth Kwabena Amponsah, PhD is a senior lecturer and head of the Department of Medical Pharmacology, University of Ghana Medical School. He has an MPhil and PhD in pharmacology. He has over 10 years' experience in teaching and research. His research focus includes clinical pharmacology (infectious disease and antimicrobial stewardship): prudent use of antimicrobials, antimicrobial level monitoring, and efficacy of antimicrobials in patients. He also has experience in therapeutic drug monitoring, population pharmacokinetic modeling, non-compartment pharmacokinetic and pharmacodynamic estimation, and pharmacokinetic evaluation of new drug formulations. He has published over 40 research articles, 3 book chapters, and several conference abstracts.

Yashwant V. Pathak has over 13 years of versatile administrative experience in an institution of higher education as dean (and over 30 years as faculty and as a researcher in higher education after his PhD). He now holds the position of associate dean for faculty affairs and tenured professor of pharmaceutical sciences at USF Health Taneja College of Pharmacy, University of South Florida and an adjunct professor at Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia. Dr. Pathak is an internationally recognized scholar, researcher, and educator in the areas of healthcare education, nanotechnology, drug delivery systems, and nutraceuticals. He has published extensively with over 50 edited volumes in the area of nanotechnology, drug delivery systems, artificial neural networks, conflict management, and cultural studies. Dr. Pathak has over 300 research papers, reviews, and chapters in books and has presented in many national and international conferences. He is also actively involved many nonprofit organizations, to mention a few, Hindu Swayamsevak Sangh (USA), Sewa International (USA), International Accreditation Council for Dharma Schools and Colleges, and the International Commission for Human Rights and Religious Freedom.

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1 Therapeutic and Toxic Concentrations of Drugs in Biological Matrices

Seth Kwabena Amponsah and Yashwant V. Pathak

Abstract

Therapeutic drug monitoring (TDM) describes the measurement of chemical parameters of drugs during clinical laboratory testing. TDM aids estimation of the efficacy and safety of drugs, often a determinant of future dosing pattern. It combines knowledge of pharmaceutics, pharmacokinetics, and pharmacodynamics of drugs. TDM typically involves measuring of drug concentration in various biological fluids (matrices). Drug levels can be assayed in blood, urine, hair, tears, etc. The concentration of drugs measured in these matrices helps to estimate whether a drug is within its therapeutic range. Usually, when drug levels in these matrices attain toxic concentrations, it will lead to potential adverse effects, thus the need for documented data on therapeutic and toxic concentrations of drugs in the various biological matrices.

Keywords

Bioanalysis · Drug levels · Matrices · Pharmacokinetics · Toxic concentration

1.1 Introduction

For several decades, drug levels in biological samples have been estimated. Estimation of levels of drugs and other toxic substances in biological matrices has proven essential in the field of medicine, toxicology, pharmacology, forensic science, and environmental research. Bioanalysis of drugs and toxic substances aids decision making in pharmacotherapy and, under certain circumstances, legal decisions [1]. Furthermore, assay of drugs in biological matrices has seen tremendous technological advancement over the years [2, 3], and this has improved the practice of this science.

Detection of drugs and metabolites in tissues can aid clinical decision in pharmacotherapy, detection of illicit drugs and foreign substances (in toxicological and forensic contexts), estimation of trace elements and toxicants in biological matrices, and estimation of foreign compounds in biological materials for signs of poison and sometimes post-mortem [4]. The equilibrium between body fluids means that a drug present in the blood will also be present in oral fluid (saliva), but this concentration may be very low, sometimes below the analytical detection limit. In other instances, low levels of drugs may be

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deposited in growing hair. It is noteworthy that drug in biological matrices may be affected by several factors, including sample collection time, sample preparation, and stability of the drug [4–7].

1.2 Therapeutic Drug Monitoring

Many decades ago, it became clear that the administered dose of a drug alone does not predict drug exposure. This prompted determination of systemic concentrations of drugs and linking this to efficacy or adverse effects. This monitoring of drug in biological matrices has made it possible to tailor drug treatment in individual patients [5].

Therapeutic drug monitoring (TDM) describes the measurement of a chemical parameter of a drug during clinical laboratory testing. This parameter can, when paired with the right medical interpretation, have a direct impact on future drug dosing [6]. TDM combines knowledge of pharmaceutics, pharmacokinetics, and pharmacodynamics. It aids in the individualization of drug dosing by keeping concentrations of drug in plasma or blood within a therapeutic range or window [7]. Clinical pharmacists and pharmacologists use pharmacokinetic principles to interpret TDM data. TDM can be used to assess compliance to drug regimen and drug-drug interactions. TDM may also be necessary when there is suspicion of toxicity, when there is subtherapeutic effect, and when the manifestations of toxicity and disease state are similar [8].

1.3 Biological Matrices

The most common biological samples used to estimate drug levels are serum, plasma, and urine [9]. Drug level assays in whole blood, saliva, and cerebrospinal fluid can also be done, albeit less frequently. Drug concentrations in different biological matrices will not be the same since the drug is not uniformly distributed within the body [3]. Characteristics of the various biological matrices are summarized in Table 1.1.

1.3.1 Blood

Due to advancements in sample preparation, chromatography, and detection techniques, whole blood may be used as a screening matrix for drugs [10]. In one matrix, both identification and quantification can be done. Blood is a very uniform matrix because physiological factors vary within restricted boundaries. Serum, plasma, and whole blood are among the most important matrices in TDM [11]. Measurement of plasma or blood concentration may be a useful surrogate or indicator of the body's exposure to drugs [8].

Sampling of blood for TDM should be done steady state, which generally occurs at least five half-lives into dosage regimen [12]. If a loading dose is administered, steady state could be reached earlier. Before steady state is reached, however, patients with hepatic or renal impairment should be monitored to ensure that they do not experience drug toxicity [8].

1.3.2 Urine

Urine sample is more commonly used than blood to test for drugs of abuse [13]. The collection of urine and analysis of drug are relatively easy to undertake. A urine sample will test positive for a drug over a longer period than blood. Drug metabolites or the parent moiety can be found in urine for several days after a single dose [14]. There are countless applications of urinary drug determination in literature, even if a significant part of them may only be of toxicological importance. However, assaying drugs in urine can be used in several contexts [15–17].

Two of the main drawbacks of TDM using urine are inconvenience of collecting samples and the possibility of a loss of integrity. Unless urine voidance is observed, the authenticity of the sample can be questioned. It has been widely documented that urine adulterated with chemicals or diluted can lead to misleading results [18]. Witnessing the collection of samples is essential to prevent adulteration. However, this can be an extremely time-consuming and impractical sometimes [19].

Table 1.1 Characteristics of different biological matrices

Characteristic	Blood	Urine	Saliva	Hair
Maximum drug detection time	1–2 days	2–4 days	1–2 days	3–6 months
Intrusive sampling	Yes	Yes	No	Yes
Potential for adulteration	None	High	Low	Medium
Refusal rate	High	Medium	Low	High

1.3.3 Saliva

Water constitutes almost 99% of saliva, a viscous oral fluid. Additionally, saliva contains salts, enzymes, peptides, hormones, lipids, sugars, epithelial cells, food fragments, and microorganisms [20, 21]. In addition to maintaining the mucosa, saliva also aids in chewing, mineralization of teeth, regulating microorganisms, enhancing taste, and digestion [22].

Oral fluids are now being considered as viable candidates for TDM, despite their limited use in the past due to numerous restrictions [23]. Direct expectoration (spitting) is a good way to collect large amounts of saliva (more than 1 ml). Alternatively, saliva collectors in the form of absorbing pads, wipes, or sponges may also be used [22].

In pharmacokinetic studies, the use of saliva is advantageous because saliva contains fewer proteins than plasma [24]. Thus, a drug is less likely to bind to proteins in saliva. It is, therefore, possible to quantify the biologically active forms of unbound drugs (or their metabolites) [25]. In addition to providing noninvasive sampling and a great number of samples, saliva can be recovered from different types of patients (sometimes critically ill ones) [26]. In some cases, saliva is considered a substitute for urine samples in toxicology, since there is less chance that the patient will deliberately adulterate the sample [27]. Nonetheless, saliva samples are smaller than blood and urine samples; hence, drug concentrations can be substantially low [22]. The analytical method used in assaying saliva samples must be able to identify and quantify several analytes from a small sample volume at low concentrations, which places some constraints on the sample [28].

1.3.4 Cerebrospinal Fluid (CSF)

Using alternative matrices to conduct TDM can reduce pain, stress, and the general invasiveness of sampling. However, it is sometimes necessary to conduct highly invasive sampling to assess drug disposition over time [29]. The CSF is one of the most important sites for drug delivery because the blood-brain barrier (BBB) can vary the ratio of CSF to plasma concentration for many drugs [23]. The study of drug levels in the CSF and directly in the brain has helped characterize compartmental pharmacology of drugs used for diseases of the central nervous system [30].

Drugs injected at clinically safe doses must be able to penetrate the brain and CSF for effective treatment of brain or meningeal diseases. Knowing the concentration of a drug at the site of action (on-target or off-target) can assist in guiding pharmacokinetic and pharmacodynamic evaluations, which in turn guides dosing decisions. The brain and CSF are not readily or repeatedly accessible compartments, and given that plasma and CSF clear drugs differently, the dynamics of drug concentrations in CSF cannot be accurately predicted or extrapolated from plasma concentration data [31, 32].

1.3.5 Hair

Human hair consists of hair shaft and hair follicle. Unlike the hair shaft, which consists of dead keratinized epithelial cells, the hair follicle contains live epithelial cells. An intricate network of blood capillaries surrounds each hair follicle, supplying it with nutrients. Each hair follicle is directly connected to the sebaceous gland (oil gland). There are three axial layers in every hair

shaft: the medulla (inner layer), cortex (middle layer), and cuticle (outer layer). There are 65–95% proteins in the hair matrix, mainly keratins, water, lipids, and minerals [33].

Hair analysis may provide evidence of drug use over an extended period. Blood and urine concentrations can only reflect use of drugs over hours and days, respectively [34]. Although the specific process for drug integration into hair is unknown, it is thought that drugs enter through blood during hair development, sebum and sweat, and the external environment [35]. Blood sampling is more intrusive than hair sampling. Hair with a width of around a pencil and a weight of about 200 mg is typically taken from the back of the head [36]. The sample should be wrapped in aluminum foil and kept dry at room temperature. It is important to thoroughly decontaminate it by washing it with various solvents before drug testing.

1.4 Therapeutic Concentration of Drugs

The main goal of clinical pharmacokinetics is to improve efficacy of drugs, as well reduce toxicity. The discovery of robust correlations between systemic drug concentration and pharmacological effect has allowed clinicians to apply pharmacokinetic principles to real-life patient settings [37]. Drug concentration at the receptor site (and other tissues) can be affected by changes in the plasma drug concentration. Increasing the concentration of the drug in plasma will often lead to a corresponding increase in the concentration of the drug in most tissues [38].

The therapeutic range of a drug is the range of doses or plasma (serum) concentrations that typically leads to the desired therapeutic effect. While a patient may achieve benefit when drug concentrations are below the minimum threshold, he or she may also experience adverse effects when drug concentrations at that level continue for prolonged periods [39]. It is important to consider the benefit-to-risk ratio when determining the lower and upper limits of a treatment regimen. In the 1960s and 1970s, pharmacokinetic studies and expert opinions were used to assign therapeutic ranges to drugs [40, 41]. In general, drugs have a single therapeutic range for all indications, regardless of age, co-medication, or comorbidity.

1.5 Toxic Concentration of Drugs

Drug toxicity occurs when a drug's therapeutic effect is exceeded; nevertheless, toxic and therapeutic responses can occur at the same time [42]. The manifestation of drug toxicity could be behavioral and physiological. Drug toxicity can manifest itself behaviorally in a variety of ways, including decreased locomotor activity, loss of motor coordination, and cognitive impairment. Tissue damage, neuronal death, and hormone cycle disruptions are examples of physiological manifestations of toxicity [43]. Safety is one of the most significant challenges in drug development. Clinical trials are affected by unexpected toxicities, and post-market safety concerns can lead to the withdrawal of new drugs from the market [44]. For most drugs, there are therapeutic and toxic concentration ranges (Table 1.2).

Another principle that explains the toxic concentration of drugs is therapeutic index (TI), which compares the dose of a drug that causes therapeutic effect to the dose that causes death (in animals) or toxicity (in humans) [45]. TI can be computed in animal research by dividing the lethal dose of a drug for 50% of the population (LD_{50}) by the minimal effective dose for 50% of the population (ED_{50}), i.e., TI = LD_{50}/ED_{50}. Depending on the drug, the difference between the ED_{50} and the TD_{50} can be significant. The safer the drug, the larger the TI. A drug with a narrow TI, on the other hand, has a steep concentration-response relationship for efficacy, toxicity, or both, resulting in a relatively low risk-benefit range [42].

In clinical practice, TI can be the range of doses at which drugs are considered effective in clinical trials for a median of participants without causing unacceptable adverse reactions [47]. This range is sufficient for most drugs, so when the recommended doses of a drug are prescribed, the maximum plasma concentration and the area under the concentration-time curve are sufficiently above the minimum therapeutic concentration and below the toxic concentration [46]. It can therefore be

Table 1.2 Therapeutic and toxic concentrations of some drugs in blood

Drug	Therapeutic blood concentration (mg/L)	Toxic blood concentration (mg/L)	References
Acetylsalicylic acid (aspirin)	20–200	300–350	[48]
Alfuzosin	0.003–0.06	0.12	[49, 50]
Alprazolam	0.005–0.05 (−0.08)	0.1–0.4	[51]
Baclofen	0.08–0.4	1.1–3.8	[52]
Bisoprolol	0.01–0.1	0.2	[53]
Bromocriptine	0.1–0.3[a]	8[a]	[51]
Cabergoline	0.058–0.144[a]	0.39[a]	[51]
Candesartan	0.08–0.18 (−0.4)	0.54	[54]
Cetirizine	Appr. 0.1–0.6	2–5	[54]
Dapsone	0.5–2	10	[55]
Dexamethasone	Appr. 0.05–0.27	0.8	[56]
Ergotamine	0.36–0.42[a]	0.82[a]	[54]
Furosemide (Frusemide)	2–5 (−10)	25–30	[54]
Gentamicin	(2–) 4–10	12	[57]
Ibuprofen	15–30 (−50)	200	[54]
Levodopa (L-dopa)	0.3–2	5–20	[51]
Metformin	0.1–2	5–10	[49]
Naproxen	(20–) 50–100	200	[54]
Omeprazole	0.05–4	8	[50]
Paracetamol	(5–) 10–25	100–150	[58]
Quinine	1–7	10	[59]
Rabeprazole	0.2–1.8	3.6	[49]
Sulfasalazine	5–30	50	[49]
Tetracycline	1–5 (5–10)	30	[49]
Vancomycin	10–20	30–40	[57]
Warfarin	1–3	10–12	[60]
Zidovudine	0.1–0.3	2–3	[54]

[a]Units are in ng/mL

assumed that at recommended doses, drugs are clinically effective and are relatively safe.

1.6 Conclusion

The concentration of drugs measured in bodily fluids or tissues is important since it helps to estimate whether a drug is within therapeutic range. The most common biological samples used to determine drug levels are urine, serum, and plasma. When a decision has been made to monitor a drug's concentration, it is critical to obtain a biological sample that is clinically meaningful. Indeed, the relevance of literature on therapeutic and toxic concentration of drugs in biological matrices during drug monitoring cannot be overemphasized.

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2 Analytical Techniques for Therapeutic Drug Monitoring and Clinical Toxicology

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Abstract

Therapeutic drug monitoring (TDM) and clinical toxicology (CT) studies play significant roles in understanding and controlling the observed variabilities in therapeutic response of administered drug products, as well as proffering measures to improve the safety and efficacy of treatments that patients receive. However, the optimization of patient care through TDM continues to remain a challenge in many health jurisdictions despite the numerous advancements and progress in analytical techniques and technology. The practice of TDM and CT in the optimization of patient care is still evolving and requires a myriad of technical and material resources to achieve the needed optimal health outcomes. One of the critical elements in this endeavour is the availability of analytical techniques that are sensitive, cost effective, and high performing in terms of accuracy and precision and also possess seamless workflow. This chapter, thus, discusses the various high-throughput analytical techniques employed in TDM and CT, as well as the challenges associated with their respective applications as reported in the literature. It must be emphasized that consideration for a suitable analytical method for TDM and CT comes with careful planning and decision making. Factors to be considered include but are not limited to the availability of expertise (clinical and laboratory), equipment/instrument, the physicochemical nature of the target analyte (drug, metabolite, toxicant, or toxin), and the clinical situation presenting the need for TDM. Other important factors such as sample preparation and storage, analytical method development and validation, and interferences associated with matrix effect also require careful consideration in order to assure the reliability and quality of TDM or CT data needed for informed clinical decision.

Keywords

Analytical techniques · Bioanalysis · Clinical toxicology · Pharmacokinetics · Pharmacodynamics · Therapeutic drug monitoring

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2.1 Introduction

Therapeutic drug monitoring (TDM) involves the optimization of therapy through adjustment of dose at the individual level by monitoring concentrations of drug or drug metabolite in body fluids (e.g. blood, plasma, or serum) or a suitable physiological matrix [1, 2]. The scientific basis and practice of TDM date to 1946 with the establishment of a correlation between the pharmacological activity of a drug and its corresponding plasma concentration [3]. This scientific establishment resulted in the practice of dose adjustment for individuals with peculiar demographic and clinical characteristics, among others, to obtain optimized therapy. Such decisions, however, are premised on the fact that the pharmacological responses being observed by clinicians can be measured either clinically (e.g. in the use of analgesic or sedative drug) or with the use of an appropriate laboratory marker (e.g. in the use of lipid-lowering drug) [1, 2, 4, 5]. The situation, however, becomes a bit more complex and unpredictable when drug response cannot be easily evaluated clinically or when toxic side effects of the drug cannot be easily monitored or detected until irreparable damage has been caused. Thus, TDM can involve both the pharmacokinetic and pharmacodynamic aspects of drug action in applied pharmacotherapy. Therefore, analytical methods for the purposes of TDM should have the power to address relevant pharmacokinetic and pharmacodynamic parameters [2, 6–9].

To wit, different doses of a drug may be required by different patients/individuals in order to observe similar optimal therapeutic effects because of an individual patient's pharmacokinetic and pharmacodynamic variabilities. Different individuals absorb, distribute, metabolize, and excrete drugs after administration differently and as well are influenced by the action of a drug based on the unique characteristics of the patient [6, 7]. Beyond the pharmacokinetic and pharmacodynamic factors that influence drug action, other variables include:

(i) Suboptimal concentration of drug molecules in the plasma and at the receptor site or site of action in the patient because of potentially poor physicochemical quality of the drugs
(ii) An interruption in drug-receptor interactions and disruption of signal transduction pathways or processes [2, 6, 7, 9]

On the other hand, CT has been defined as a 'medical subspecialty focusing on the diagnosis, management, and prevention of poisoning and other adverse health effects due to medications, occupational and environmental toxins and biological agents' [10]. The strategy for CT includes among others the confirmation of the toxicant and/or poison using the appropriate analytical methods [11]. Since the dose of a drug makes it a poison, almost all drugs are studied under CT [12].

As earlier mentioned, the relevance of appropriate and sensitive analytical techniques in TDM and CT cannot be overemphasized. We propose in this book chapter that if sensitive high-throughput analytical techniques and detection technologies were more widely available, user friendly, and affordable, there would be better treatment outcomes, patient adherence, and reduced side effects for patients on certain drugs including antibiotics, anticancer agents, and immunosuppressants (cyclosporin), among others. In order to make available such simple, cost-effective, and efficient analytical methods, rigorous efforts that involve an investment of resources into analytical technology development and transfer and, more importantly, availability of resources to train and build capacity for TDM and CT implementation will be required in the global health delivery space [2, 6, 9].

Analytical techniques that have found successful use in TDM and CT can be very diverse, depending on the depth of the investigation being undertaken (i.e. the physicochemical properties of the drug, pKa values, ionized or unionized status at physiological pH, etc.), parameters

being monitored, the biological matrix (saliva, urine, plasma, etc.), and others. For instance, to establish a scientifically sound correlation between plasma drug concentration and pharmacological response, an analytical method must be developed and validated. Analytical techniques earlier employed for TDM studies included colorimetry, electrochemical techniques, spectrophotometry, and spectrofluorimetry [13–18]. Some of these methods currently find very little or no use at all in TDM studies due to their lack of specificity and inability to distinguish clear effects due to matrix from the drug of interest [13, 17]. Although such limitations exist for the majority of drugs, the application of colorimetry as well as flame atomic emission spectroscopy is still relevant for TDM of lithium [19]. Furthermore, bioassay techniques were previously used for TDM analysis of many antibiotics. However, this technique was found as laborious with poor specificity for polypharmacy patients and very slow in obtaining data required to make an informed clinical decision. The technique has also been reported as imprecise for present-day applications [2].

Thin-layer chromatography has also experienced a significant shift in its use for TDM analysis currently, as its limitations for total quantitative estimates are a challenge for such purposes [2]. Current high-throughput analytical techniques, which mostly find wide applications for routine monitoring and measurement of plasma drug concentrations, are electrophoresis, immunoassays, gas chromatography (GC), conventional high-performance liquid chromatography (HPLC), and recently, ultra-performance liquid chromatography (UPLC). The availability and compatibility of hyphenated modes such as LC-UV, LC-MS/MS, LC-MS, and GC-MS have positively impacted on sensitivities of such techniques in the successful quantitation of drug molecules in various biological matrices [2, 6, 20, 21].

This chapter focuses on a description of modern analytical techniques employed in TDM and CT, appraisal of the strengths and limitations of the various techniques described, as well as provision of some examples of relevant studies reported in the literature.

2.2 Immunoassays

These analytical techniques which involve the development and application of antibodies have found significant use in various disciplines including TDM and CT. The key aspect of the development and application of immunoassays borders mainly on antibodies. Antibodies, usually generated by beta-lymphocytes following exposure to substances such as foreign cells or proteins, required to trigger the immune system of mammals, are proteins. The main purpose of antibodies is to help fight infection in mammals. Various subtypes including IgA, IgD, IgE, IgG, and IgM have been reported and each has specific roles or functions within various compartments of the human body acting as sentinel sites in cases of re-infection or attack of new infections.

Although this technique comes with its own unique limitations (including the probability of obtaining false results, the effect of matrix on antibodies, poor specificity resulting in cross-reactivity with compounds that share similar physicochemical properties amongst others), immunoassays, with its cost effective, rapid detection, and robust nature, continue to play highly significant roles in the detection and quantification of minute amounts of target analytes in various complex matrices such as hair, plasma, and others. Immunoassays are usually designed for specific analytical purposes. For example, it could be designed and developed for solely qualitative purposes as well as for both qualitative and quantitative uses. Furthermore, it finds application for both low and large molecular weight molecules (compounds with molecular weights $\geq$250 daltons). The major common elements of interest in the design and development of an immunoassay technique include (i) target analyte (antibodies), (ii) a drug derivative needed to link to a reporter (hapten), (iii) the target for assay (analyte), (iv) required buffers or conditions such as pH of the sample, (v) a location to immobilize antibody (solid phase), (vi) the sample being analysed (matrix), and (vii) a recorder that amplifies the result (usually in the form of enzymes, fluorescence, chemiluminescence, and radioimmunoassay). Although various forms exist for

various purposes, the basic elements enumerated above remain basically the same for all immunoassay methods.

The development of such analytical techniques first involves the creation of the required antibody, followed by its production, and finally the immunoassay design. The evaluation of an antibody available for the design of the assay is a critical stage that informs the assay format that will be employed for the assay. Assay formats are generally grouped into two categories namely, (i) heterogenous and (ii) homogenous immunoassays. Heterogenous immunoassays require a separation step to remove materials that did not bind immunologically (separately bound from free materials). As an analytical method, certain key parameters required to evaluate the performance of the analytical technique under consideration include specificity/cross-reactivity, precision, limit of detection, interferences/adulteration, and stability. The optimization of such parameters assures the quality of data obtained from such determinations [2, 22–27].

Examples of compounds that have undergone TDM and reported in the literature employing various immunoassay techniques include immunosuppressants [28, 29], antiepileptic drugs [30–32], antibiotics [30, 33–36], bronchodilators [30], antimalarial agents [37], psychotropic drugs [38, 39], cardiovascular agents [40], anticancer agents, [35, 41, 42], and monoclonal antibodies [43–45] (Table 2.1). Also, immunoassays have been used in CT studies of diverse drugs [46].

Table 2.1 Analytical methods for TDM and/or CT of drugs

Analytical method	Analyte	Reference
Immunoassay	Immunosuppressants	[28, 29]
	Antiepileptic drugs	[30–32]
	Antibiotics	[30, 33–36]
	Bronchodilators	[30]
	Antimalarial agents	[37]
	Psychotropic drugs	[38, 39]
	Cardiovascular agents	[40]
	Anticancer agents	[35, 41, 42]
	Monoclonal antibodies	[43–45]
Electrophoresis	Antiepileptic drugs	[31, 32, 47, 48]
	Inflammatory bowel disease drugs	[49]
	Nonsteroidal anti-inflammatory drugs	[50, 51]
	Cardiovascular drugs	[47]
	Psychotropic agents	[47, 52]
	Diuretics	[47]
	Vasodilators	[47]
	Antibiotics	[53]
	Anthelmintics	[54]
	Anaesthetic agents	[55]
Biosensors	Anticancer agents	[56–59]
	Anticoagulants	[60]
	Monoclonal antibodies	[61–63]
	Antibiotics	[64–72]
	Bronchodilators	[73]
	Anticonvulsants	[74]
	Substance of abuse	[75]
HPLC/UPLC	Anti-infective agents	[76]
	Immunosuppressants	[28, 77–83]
	Antifungal agents	[81, 83, 84]
	Anti-arrhythmic drugs	[85]
	Monoclonal antibodies	[86]
	Antibiotics	[21, 83, 87–89]
	Antiepileptic drugs	[31, 32, 83, 90, 91]
	Anticancer drugs	[42, 83, 92, 93]
	Antiviral agents	[83, 94]
	Cardiovascular drugs	[83]
	Psychotropic agents	[38, 83, 95–105]
	Anticoagulants	[83]
	Antidiabetic agents	[83]
	Substance of abuse	[97]

2.3 Electrophoresis

Electrophoresis is a separation technique involving the use of a high-voltage electric field (electro-driven) to migrate and separate charged particles in a capillary-shaped separation compartment. Efficient separations resulting from capillary electrophoresis (CE) are usually employed in the analysis of charged compounds or drug molecules under the influence of an electric field generated uniformly across the separation compartment. The application of this technique especially in TDM is influenced by certain unique features that CE provides, and these include robustness of the instrument with

its high separation efficiency and sensitivity and minimal application of samples (sample size) and solvents, coupled with the versatile nature of its applications. The above-mentioned applications together with highly improved resolution, decreased separation time, and automation of the instrument provide the required real-time detection needed for such sensitive tasks. The principle of electrophoresis involves the high-voltage influenced migration of charged species between oppositely charged electrodes, dependent on electrostatic and electroosmotic forces. Three key parameters (i.e. size, charge, and shape of the analyte of interest) significantly influence the efficiency of separation. The commonly encountered CE modes are capillary gel electrophoresis (CGE), capillary isoelectric focusing (CIEF), capillary electrochromatography (CEC), capillary zone electrophoresis (CZE), and micellar electrokinetic chromatography (MEKC). Quite a significant number of drug molecules have had their levels in biological matrices measured using these named modes or techniques in TDM studies. Though CZE finds extensive use and application in TDM, all the other modes of separation are also utilized as appropriate for some drug molecules. It is also worth mentioning that hyphenation of CZE mode with mass spectrometry detectors is made possible through efficient compatibility and this further enhances structural elucidation for metabolite profiling [2, 106–108]. It must also be noted that of all the advantages listed for CE in TDM, some limitations do exist for its application, and these include the tendency of target analytes to undergo adsorption (which can be reversible or irreversible) onto the negatively charged surface of silica-based capillaries. It is as well difficult in handling the very small sample sizes and volumes with precision.

Electrophoretic methods have been used for the TDM of antiepileptic drugs [31, 32, 47, 48], inflammatory bowel disease drugs [49], nonsteroidal anti-inflammatory drugs [50, 51], cardiovascular drugs [47], psychotropic agents [47, 52], diuretics [47], vasodilators [47], antibiotics [53], anthelmintics [54], and anaesthetic agents [55] (Table 2.1). CT studies have been reported for different drugs using electrophoretic methods [109].

2.4 Biosensors

Biosensor-based techniques use antibodies, enzymes, membranes, molecularly imprinted polymers, and aptamers for the recognition of analytes of interest based on binding affinity [110]. Biosensors may be classified as either electrochemical, optical, piezoelectric, or nanomechanical [110]. This technique is advantageous due to low sample consumption, nearly non-invasive sample collection procedure, reduced reagent consumption, reduced analysis time, multiple analyte detection, and portability [111]. These advantages notwithstanding, there are challenges associated with sensitivity, qualitative, or semi-quantitative results obtained with the use of biosensors for TDM [112].

Biosensors have been used for the TDM of anticancer agents [56–59], anticoagulants [60], monoclonal antibodies [61–63], antibiotics [64–72], bronchodilators [73], anticonvulsants [74], and opioids [75] (Table 2.1). Biosensors have also been applied in CT studies [113].

2.5 Conventional HPLC and Emerging UHPLC Techniques

For decades, HPLC and recently (from the first decade of the twenty-first century) UHPLC have seen significant applications in various disciplines for the efficient separation and quantification of various analytes in various matrices. The ability of this unique and versatile technique to separate and analyse complex samples, both small and large molecules, continues to gain prominence in almost all basic and applied sciences of which TDM is no exception [114–119].

These liquid chromatography techniques have found versatile application and use in diverse settings as a result of its ability to separate a wide range of sample types, exceptional resolution power, speed of separation, and compatibility with a wide scope of highly sensitive detectors including mass spectrometric detectors. Such advantages that conventional HPLC as well as emerging UHPLC techniques provide have influ-

enced their high use and applications in forensic, biological, and pharmaceutical research including TDM and CT [2].

Both conventional HPLC and UHPLC have similar mechanisms of separation and resolution. However, when analysts and scientists in various fields wish to have faster separation without compromising data quality, then UHPLC becomes the obvious choice for such tasks. UHPLC also provides the requisite technological improvements in stationary support material (column) chemistry, detectors, and overall hardware required for ultra-fast separation without compromising the quality of data obtained.

The efficient separation of components of different samples could be due to the availability of diverse modes of separation including adsorption, partition, ion exchange, and size exclusion. The selection of the mode of separation usually depends on the type of task to be performed and the physicochemical properties (polar or nonpolar nature, etc.) of the analyte. Thus, a wide range of options with respect to the mode of separation such as normal phase, reversed phase, ion exchange, or size exclusion chromatography are available for well-defined tasks. The sensitivity of such analytical methods would depend on the type of detectors employed to monitor the column eluates, and these could be optical detectors such as ultraviolet (UV) absorption, fluorescence, diode array, and photodiode array detectors. It must be noted that the diode array (DAD) and photodiode array (PDA) detectors are advanced forms of UV detectors. Other equally well-known detectors include refractive index and electrochemical detectors (two types, namely, the coulometric detector and amperometric detector).

The development and introduction of hyphenated techniques especially with mass spectrometric detectors some decades ago have also seen significant improvement in the ability of conventional HPLC and UHPLC to separate and identify samples in highly complex matrices such as observed in TDM, and these include HPLC-MS, LC-MS/MS, and UPLC-MS/MS [2, 117].

Further to all of the above advancements, the availability of using a solvent system with constant composition for an entire analysis (isocratic mode) or being able to change/modify the composition of the solvent system for analysis with time (gradient mode) provides the required elution modes for efficient separation of compounds in even highly complex matrices.

However, there are several other factors that may influence the reliability of HPLC/UHPLC data for TDM and CT. These include the nature of the matrix being studied (urine, blood, liver, saliva, etc.), probable interference from endogenous substances/compounds from the matrix, the levels of the analyte available for detection and quantification (sensitivity of the detector being employed), and nature of sample preparation procedures used prior to pre-concentration of sample and analysis [2, 115].

Examples of drug compounds for which TDM has been performed and reported in literature with the use of the liquid chromatography technique include anti-infective agents [76], immunosuppressants [28, 77–83], antifungal agents [81, 83, 84], anti-arrhythmic drugs [85], monoclonal antibodies [86], antibiotics [21, 83, 87–89], antiepileptic drugs [31, 32, 83, 90, 91], anticancer agents [42, 83, 92, 93], antiviral agents [83, 94], cardiovascular drugs [83], psychotropic agents [38, 83, 95–105], anticoagulants [83], antidiabetic agents [83], and substance of abuse [97] (Table 2.1). CT studies of drugs using liquid chromatography have also been reported in the literature [11, 120–122].

2.6 Gas Chromatography (GC)

This analytical technique, which also borders on partition chromatography, has similarities to the HPLC technique already described. However, there are some significant differences with respect to the instrumentation, stationary phase support material (column), the mobile phase, and the nature of analytes. In GC, compounds suitable for analysis must be volatile in nature or if not volatile can be derivatized to provide samples that can be volatilized during analysis without thermal decomposition because of the high temperatures utilized in

such analysis. Unlike HPLC, the GC separation is ensured and performed on a stationary phase which is usually a steel capillary tube that is supplied with a continuous flow of inert gases or supercritical fluid (SCF) as a mobile phase in a temperature-regulated oven (usually around 400 °C). The mode of separation could be gas-solid or gas-liquid in nature, depending on whether the column contains either a solid (polymers) or liquid (polysiloxanes) stationary phase [2, 117].

The detection of compounds is successfully achieved using any of the following detectors:

(i) Nitrogen-phosphorus detector
(ii) Alkali flame ionization detector
(iii) Electron-capture detector
(iv) Atomic emission detector
(v) Flame ionization detector

Hyphenated modes with MS detectors are also available for GC in TDM analysis. Limitations such as lack of regular preventive maintenance and the presence of even trace levels of contaminants in the mobile phase (carrier gas), among others, could result in significant variabilities in data acquisition. Due to this challenge, few drug compounds have had their TDM studies reported in literature with the use of GC due to the huge tasks associated with the monitoring and control of variabilities in data acquisition.

Examples of drug compounds for which TDM data has been determined and reported with the use of GC include antiepileptic drugs [31, 32], psychotropic drugs [123–125], antihistamines [126], and narcotic analgesics [127] (Table 2.1). GC has also been applied in CT studies [128].

2.7 Conclusion and Outlook

In actualizing the cost benefits of TDM in clinical settings, it is imperative to re-emphasize the versatility of TDM in the establishment of benchmarks for individualization of therapy, dose optimization, screening for drug interactions, and prevention of drug toxicity. The objectives of any TDM project should be clearly defined in order to make room for appropriate decisions on the optimal selection of techniques and instrumentation to generate the required data for clinical interpretation and application. TDM should have comprehensive sample collection and handling protocols in addition to overarching quality control measures to govern sample analysis, data acquisition, data interpretation, and data management. The continuous introduction of novel and more efficacious drugs for the treatment of diseases, which can also be potentially toxic, further strengthens the need to have clinical and analytical mechanisms to improve drug therapy. For this purpose, advances in the various analytical techniques and related instrumentations for TDM and CT have led to the availability of many analytical tools with diverse costs and complexity as already described. Among the several analytical techniques, the immunoassay technique appears to be the most commonly used, with a lot of immunoassay kits commercially available. However, this technique might not be suitable in multicomponent analyses, especially in paediatrics where small sample volumes are used to monitor multiple analytes. Under such circumstances, the HPLC/UHPLC technique and its hyphenated forms are considered more appropriate because of the capacity to analyse and detect multicomponent analytes in a sample with a highly acceptable level of accuracy and precision, even when certain analytes co-elute (when mass spectrometric detection is applied). As a result of this, the HPLC/UHPLC technique has been shown to be suitable for a wide scope of drugs and matrices. Though the initial capital investment into the liquid chromatographs is high, they are known to have low running costs, making them a prudent choice for resource constraint environments that may need TDM to enhance therapeutic and clinical outcomes. Despite its limited role in TDM as a result of potential variabilities in data acquisition, GC has been very useful in CT screening, especially in its hyphenated modes (GC-mass spectrometric detection).

With the assessment of the advantages and disadvantages of the other analytical techniques for TDM and CT studies, an appropriate decision can be taken on optimal technique and instru-

mentation for any clearly defined TDM or CT programmes. It is still unclear when TDM will become routine in the health systems of emerging economies.

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