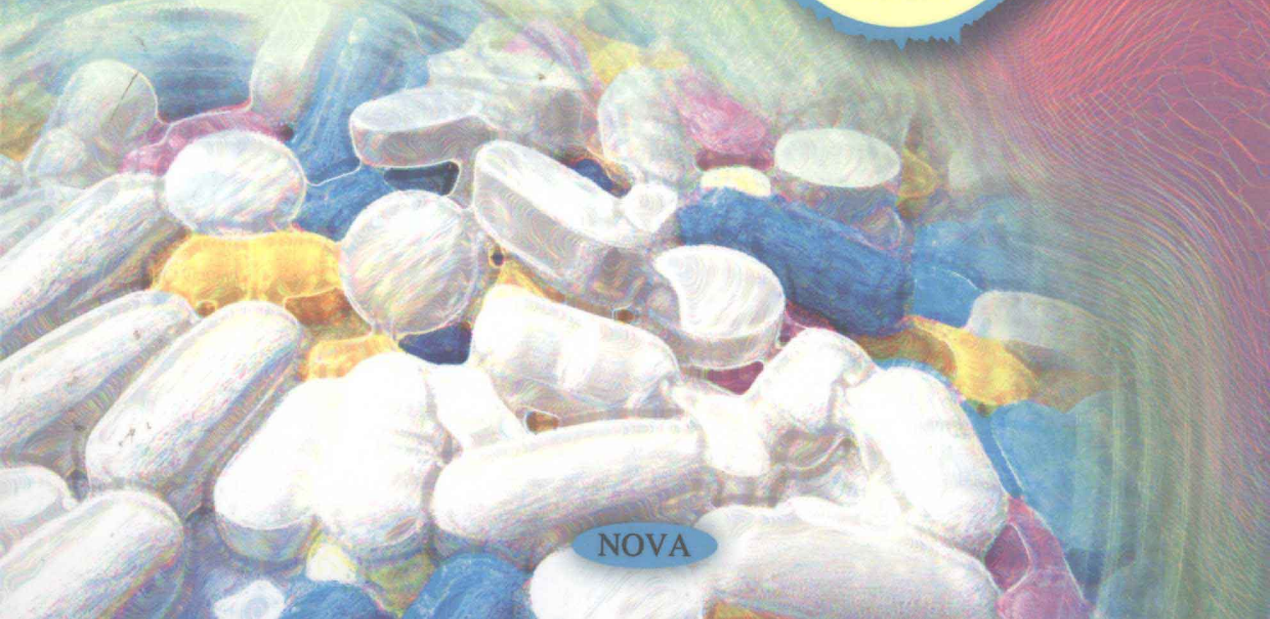
Boris Andreev
Vasily Egorov
Editors

HANDBOOK OF DRUG TARGETING AND MONITORING

Pharmacology-Research, Safety Testing and Regulation Series



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HANDBOOK OF DRUG TARGETING AND MONITORING

BORIS ANDREEV
AND
VASILY EGOROV
EDITORS

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PREFACE

Drug monitoring in clinical chemistry refers to the measurement of drug concentration in blood serum/plasma so that an optimal concentration is obtained to benefit patients with minimal toxic adverse effects. Drug delivery systems have been developed for enhancing the pharmacokinetic profile of any given active agent, increasing the accumulation at the target site, while minimizing their systemic distribution. Magnetic colloids, for example, are very promising stimuli-sensitive drug delivery systems because of their magnetic-field responsiveness. This book describes the main synthesis strategies and surface functionalization processes of magnetic colloids, giving an overview of the recent developments in magnetic drug targeting. The possibilities of very promising strategies for controlling the biodistribution profiles of chemotherapy agents are also investigated, including passive and active targeting strategies involving the use of drug carriers. Other chapters in this book examine the application of nanotechnology in pharmacotherapy, therapeutic drug monitoring (TDM) of antiepileptic drugs (AEDS), a mathematical modeling approach to testing drug effects on Hepatitis C virus (HCV), and the recent developments in drug monitoring by high performance liquid chromatography (HPLC).

Chapter 1 - Current anti-cancer drugs have little or no specificity for tumor cells, resulting in low concentrations at the cancer region (inefficacy), systemic toxicity and severe side effects. In order to beat this challenge, the development of anti-tumor drug delivery strategies has been proposed to improve drug localization at the tumor region and, therefore, to increase the anti-cancer efficacy, while reducing the systemic side effects. In this chapter, the possibilities of very promising strategies for controlling the biodistribution profiles of chemotherapy agents are investigated: passive targeting (through the enhanced permeability and retention effect) and active targeting (including ligand-mediated delivery and stimuli-sensitive carriers) strategies, involving the use of drug carriers.

Chapter 2 - The use of a drug is often limited by its poor specificity and selectivity, usually leading to the failure of pharmacotherapy and a high incidence of severe drug-associated side effects. Drug delivery systems have been developed for enhancing the pharmacokinetic profile of any given active agent, increasing the accumulation at the target site, while minimizing their systemic distribution. Stimuli sensitive carriers, as a part of the active drug targeting strategies, allow selective drug delivery to specific organs or tissues. These colloidal systems are engineered to be able to change their physical properties under exposure to an external stimulus, leading to a significant enhancement of the drug concentration at the target region before allowing its release.

Magnetic colloids are very promising stimuli-sensitive drug delivery systems because of their magnetic-field responsiveness: an applied magnetic field can concentrate them at the desired site, keeping it there for a given period of time until the drug is totally released. These systems are usually made of a magnetic core and a biodegradable polymer shell. Typically, the magnetic core will allow the accumulation of the colloid in target region by means of a magnetic field. Meanwhile, the polymeric shell will play the role of transporting the drug to the target site, releasing it there during its biodegradation. This chapter describes the main synthesis strategies and surface functionalization processes of magnetic colloids, giving an overview of the recent developments in magnetic drug targeting. Finally, other very interesting *in vitro* and *in vivo* applications of these magnetic colloids are also briefly described.

Chapter 3 - One of the challenges in determining appropriate drug targets in neuropsychiatric diseases is determining whether there is a core dysfunction that is responsible for the development of other disease symptoms. Attention impairments are thought to be core cognitive deficits in Alzheimer's disease and schizophrenia. In rats, an attention-demanding task has been developed that requires discrimination of visual signals from "blank" trials when no signal is presented. Several experiments using this task have demonstrated that basal forebrain corticopetal cholinergic neurons are necessary for normal attentional processing. For example, lesions of corticopetal cholinergic neurons decrease signal detection in this attention-demanding task. There is a loss of basal forebrain corticopetal cholinergic neurons during early stages of Alzheimer's disease. Data from our laboratory have suggested that muscarinic receptors, in particular the M1 receptor, are critical for some of the attentional functions mediated by acetylcholine. Decoupling of the M1 receptor from its associated G-protein has been reported in patients with Alzheimer's disease. As a result of this decoupling, important downstream effects may not be occurring following binding to the M1 receptor. This decoupling may explain why acetylcholinesterase inhibitors are beneficial for a limited time period for patients with Alzheimer's disease. Lower levels of protein kinase C (PKC) correlate with M1/G-protein decoupling. PKC activation may be an important therapeutic approach for alleviating cognitive deficits in Alzheimer's disease.

Alterations of attentional processing are also thought to represent a core cognitive deficit in schizophrenia. In animal models, manipulations including N-methyl-D-aspartate (NMDA) receptor blockade or repeated amphetamine administration, can be used to mimic some of the brain changes in schizophrenia. It has been shown that cortical acetylcholine is substantially elevated by these pharmacological manipulations. In our laboratory, NMDA receptor blockade or exposure to escalating doses of amphetamine have been shown to impair attentional performance, decreasing accuracy on "blank" trials when no visual signal is presented. These findings correspond with other experiments indicating that manipulations that "overactivate" basal forebrain corticopetal cholinergic neurons lead to increased errors on blank trials. These data suggest that cortical cholinergic functioning may represent an important target for treating the cognitive symptoms in schizophrenia. Recent data have suggested that many of the effects of antipsychotics are mediated through the cholinergic system, in particular, M1 receptors. Partial M1 receptor agonists may represent an important new step in treating attentional deficits in schizophrenia. Finally, the authors provide some evidence that PKC activity is altered in schizophrenia.

Chapter 4 - Dragon's Blood is one of the renowned traditional medicines with analgesic activity. It could be obtained though the alcoholic extraction of the special resinous parts of

Dracaena cochinchinensis (Lour.) S. C. Chen. In order to determine the molecular target for analgesic effect of Dragon's Blood and its chemical component acting on the molecular target, its modulation on the tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) voltage-gated sodium currents in the freshly isolated dorsal root ganglion (DRG) neurons of Wistar rats were verified by using patch clamp technique. Based on it, a novel analgesic mechanism which was different from the traditional knowledge about analgesic effect caused by anti-inflammatory was proposed. That is Dragon's Blood could directly interfere with the transmission of nociceptive information in primary sensory neurons by modulating sodium channels. And it was determined preliminarily that the modulation of Dragon's Blood on the two types of sodium currents was caused by the combined effect of its three components (cochinchinenin A, cochinchinenin B, and loureirin B) on voltage-gated sodium channels. As all the three components have the same characteristic group as capsaicin by which vanilloid receptor 1 (VR1) can be activated, in order to further clarify the mechanism of the modulation of the three components on the voltage-gated sodium channels, the inhibition of cochinchinenin B, loureirin B and the combination of low doses of the three components on the capsaicin-evoked currents and the competitive effect between the capsaicin and loureirin B when they modulated the voltage-gated sodium currents were verified by using patch clamp technique in DRG neurons of Wistar rats. From these results it could be inferred that there are at least two molecular targets for analgesic effect of Dragon's Blood. One is voltage-gated sodium channel and the other is VR1. It seems that there is interaction between the two molecular targets. In order to confirm the molecular target and the material basis for the analgesic effect of Dragon's Blood at systemic level, extracellular microelectrode recordings were used to observe the effects of Dragon's Blood and various combinations of cochinchinenin A, cochinchinenin B, and loureirin B on the discharge activities of wide dynamic range (WDR) neurons in spinal dorsal horn (SDH) of intact male Wistar rats evoked by electric stimulation at sciatic nerve. The interactions between the three components in modulating the evoked discharge activities of WDR neurons were also evaluated. Results of extracellular microelectrode recordings showed that Dragon's Blood inhibited the discharge frequencies of WDR neurons evoked by electric stimulation at sciatic nerve in a concentration dependent way and the synergistic combined effect of cochinchinenin A, cochinchinenin B and loureirin B on the evoked discharge of WDR neurons was similar to that of Dragon's Blood. In addition, in order to make Dragon's Blood and its components reach voltage-gated sodium channel and VR1, a novel targeting drug delivery system was prepared. The system is a novel composite system with pumping effects which is made by the implantation of a composite structure with intelligent functions in the microcapsule. The specific pump will effectively increase the efficiency of the drug quantitatively reaching the molecular target by using intelligent biomaterials and the principle of compress pump.

Chapter 5 - A method to develop multifunctional hybrid mesoporous silica potentially useful for drug targeting has been introduced starting from neutral surfactant-templated mesoporous silica. Folic acid, a receptor specific ligand, able to be recognized by specific tissues, has been covalently coupled on the external surface of mesoporous silica thanks to the presence of aminopropyl groups previously linked to mesoporous silica through direct insitu or post-synthetic hybridization procedure. A series of hybrid materials, useful to investigate the complex structure of folate-derivatized mesoporous particles by comparing NMR and FT-IR spectroscopic results, have been developed starting from a silica gel substrate derivatized with amino-propyl functionality and successively coupled to folic or heptanoic acid. FT-IR

spectroscopy as well as NMR results unambiguously showed that amide covalent bond is successfully achieved through the use of carbodiimides type reagents, typically used in peptide synthesis. Folic acid has been retained on the surface of functional mesoporous silica either when carbodiimide reactant is used or when the same preparation is carried out without carbodiimide; in the latter case it is removed after HCl treatment showing that folic acid was retained by electrostatic interaction and by van der Waals forces. One of the materials, after surfactant extraction, has been charged with cisplatin, an anticancer agent. The diffusion profile in a simulated body fluid showed that cisplatin is gradually released within 6 hours. Fluorescent folic acid-particles, obtained through post-synthetic hybridization procedure, have been tested in tumor cell cultures to verify, through confocal microscopy, their ability to be internalized by cells.

Chapter 6 - Some of the main problems associated with systemic drug administration concern biodistribution of pharmaceuticals throughout the body including: non-specific or low affinity towards the pathological site; the necessity of a large total dose of drug to achieve high local concentration; non-specific toxicity and adverse side-effects due to high drug dosage. Today, one of the currently studied approach to resolve many of these problems is drug targeting, i.e. the induced drug accumulation in the target zone of the body, independently on the method and rout of administration. Actually, the method which provides the widest opportunities to this approach is the use of specific molecules, i.e ligands having an high affinity towards the cells of the area of interest. These targeting ligands are successfully linked to drug delivery systems, either in the micrometer or nanometer scale, such as microparticles, nanoparticles, polymeric micelles, dendrimers, polymeric conjugates, and supramolecular multifunctional systems as well. The results obtained by these systems, in term of in vitro and in vivo targeting efficiency have been in many cases very promising. Folic acid, a high affinity ligand of the folate receptors, is one of the most successfully proposed targeting ligand for specific tumor drug delivery. This because folic acid retains its receptor binding properties when derivatized or conjugated via its γ-carboxyl; therefore, folate conjugation represents a suitable and valid method of targeting a drug towards folate receptor expressing cells. In this chapter, a systematic approach for the conjugation of folic acid to polymers to obtain folic acid-polymeric conjugates as components of colloidal drug delivery systems is given.

Chapter 7 - Hepatitis C virus (HCV) is a human pathogen causing severe liver diseases. Its high prevalence, unavailability of a prophylactic vaccine and the disappointing efficiency of current therapies pose challenges for the biomedical sciences. Most efforts to develop antiviral agents for HCV have focused on the inhibition of key viral enzymes (NS3 protease, NS5B polymerase) and of translation initiation of the viral genome. Mathematical modeling appeared to be a good approach to testing drug effects on HCV replicon replication in a cell. The authors have previously formulated an experimental data-based mathematical model for suppressive effect of subgenomic HCV replicon replication in Huh-7 cells in the presence of potential individual drugs. The model involves the mechanisms of the action of inhibitors leading to blockage of the steps of HCV replicon translation, polyprotein processing, and replication of the HCV strand RNAs. Using the model, the minimal treatment time for clearance of Huh-7 cells from HCV RNA in the presence of individual inhibitors acting on various viral targets was estimated. Based on comparisons of this parameter for drugs acting with the same affinity on various viral targets, NS5B polymerase was identified as the optimal target. The minimal inhibitor dose that might be administered before the transfection point in Huh-7 cells

to protect infection generation was calculated. Comparisons of the doses the authors estimated for drugs of different types showed that the preventive action of inhibitors on translation initiation is preferable.

Chapter 8 - Lysophosphatidic acid (LPA) is an epochal lipid found in normal human circulation that has a multitude of signaling consequences in the cell and outcomes influencing the biological system. At least nine receptors are known to the agonist LPA and these are endogenously and pervasively expressed throughout the body. LPA is involved in the progression of ovarian cancer and LPA receptor expression is implicated in the aggressiveness of this disease. Pharmacological inhibitors for LPA production are in development and will likely reach clinical trials. Foremost leading targets are LPA itself and the enzyme that generates LPA, autotaxin. Although no known toxicities have been observed or reported in mice using short-term experimental therapeutics targeting the LPA pathway, it is important to consider potential adverse effects that could arise as a result of systemic, long-term LPA-targeted therapies in humans. Here the authors highlight major considerations that need to be measured and addressed as these drugs move towards pre-clinical and clinical trials, such as wound healing, the immune system response, physical appearance and cardiovascular functioning. While there are a number of diseases that could benefit from LPA signaling intervention, adverse effects are a major concern with all drugs. This report scrutinizes observations at the molecular level resulting from LPA signaling and intervention in order to predict adverse effects and improve patient management during clinical trials.

Chapter 9 - Cytochrome P450 (CYP) 3A4 is the most abundant hepatic and intestinal phase I enzyme that metabolizes approximately 50% marketed drugs. A number of important drugs have been identified as substrates, inducers and/or inhibitors of CYP3A4. The ability of drugs to act as inducers, inhibitors, or substrates for CYP3A is predictive of whether concurrent administration of these compounds with a known CYP3A substrate might lead to altered drug disposition, efficacy or toxicity. The substrates of CYP3A4 considerably overlap with those of P-glycoprotein (P-gp). To date, the identified clinically important CYP3A4 inhibitors mainly include macrolide antibiotics (e.g., clarithromycin, and erythromycin), anti-HIV agents (e.g., ritonavir and delavirdine), antidepressants (e.g. fluoxetine and fluvoxamine), calcium channel blockers (e.g., verapamil and diltiazem), steroids and their modulators (e.g., gestodene and mifepristone), and several herbal and dietary components. Many of these drugs are also mechanism-based inhibitors of CYP3A4. A small number of drugs are identified as inducers of CYP3A4. The inhibition or induction of CYP3A4 by drugs often causes unfavorable and long-lasting drug-drug interactions and probabaly fatal toxicity, depending on many factors associated with the enzyme, drugs and the patients. Clinicians are encouraged to have a sound knowledge on drugs that behave as substrates, inhibitors or inducers of CYP3A4, and take proper cautions and close monitoring for possible drug interactions when using drugs that are CYP3A4 inhibitors or inducers.

Chapter 10 - Drug monitoring in clinical chemistry refers to the measurement of drug concentration in blood serum/plasma so that an optimal concentration is obtained to benefit patient with minimal toxic adverse effects. Drug monitoring addresses drugs with narrow effective range or a narrow therapeutic/toxic index. It is required to individualise and optimise drug therapy. Moreover it supports pharmacokinetic and drug metabolism studies.

Drugs that usually require monitoring include: cardioactive medications, antiepileptic drugs, antibiotics (e.g. aminoglycosides), anti-cancer drugs, immunosuppressants,

antidepressants (e.g. tricyclic antidepressants), bronchodilators (Theophylline), antipsychotics etc.

Monitoring of medication is also important to detect poisoning with above drugs in forensics.

In pharmacology, many drugs are used without monitoring of blood levels, as their dosage can generally be varied according to the clinical response of the patient. In some drugs insufficient levels will lead to undertreatment or resistance, and excessive levels can lead to toxicity and tissue damage.

The available analytical methods for monitoring drug levels in patient specimens in human blood or serum/plasma include: immunoassays, such as microparticle enzyme immunoassay (MEIA), enzyme multiplied immunoassay technique (EMIT), fluorescent polarization immunoassay (FPIA), radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) and most frequently fluorescence polarisation immunoassay (FPIA) and liquid chromatography-based methods. Chromatography-based methods include high performance liquid chromatography (HPLC) with ultraviolet detection, HPLC-mass spectrometry (HPLC-MS), and HPLC-tandem mass spectrometry (HPLC-MS/MS). In clinical practice, immunochemical assays are applied to screen the drugs in biological fluids. These assays while they are sensitive, they are not sufficiently selective and can only be used to eliminate negative samples. Confirmation of the initial screening should always be implemented by a separation assay usually a chromatographic one, which should have sufficient sensitivity and selectivity to confidently identify the analyte down to the cut-off level.

Currently HPLC-MS/MS has gained increasing popularity in clinical laboratories due to the advantages of the technology over other methods, while the capital cost for instruments has been decreased. HPLC-MS/MS provides high specificity and sensitivity for the simultaneous measurement of several drugs and/or their major metabolites in one single analytical run.

In this text chromatographic methods published in the last decade are reviewed regarding their applicability to drug monitoring.

Chapter 11 - Warfarin is one of the most commonly used anticoagulant drugs worldwide with a role in the treatment for a variety of conditions, such as atrial fibrillation, artificial heart valves, deep venous thrombosis, pulmonary embolism and antiphospholipid syndrome. It exerts its anticoagulant effect by interference of the vitamin K mediated γ-carboxylation of the coagulation factors II, VII, IX and X, rendering them dysfunctional by compromising their phospholipid-binding properties. Although effective as an anticoagulant drug, care must be taken in warfarin administration as it interacts with many commonly used medications and some foodstuffs. Additionally, it has a narrow therapeutic range so frequent monitoring with blood tests coupled with expert dose management are crucial to patient safety.

Laboratory monitoring is achieved almost exclusively by use of the prothrombin time (PT). The raw data is converted to the International Normalised Ratio (INR), calculated by division of the patient's clotting time by the local analytical system geometric mean normal PT to generate a PT ratio. This ratio is then taken to the power of a mathematical expression of the sensitivity of the thromboplastin reagent to the warfarin effect relative to an international standard, the International Sensitivity Index (ISI). Theroetically, the INR system should compensate for the inevitable differences in raw clotting times between the vast array of available reagents and analytical platforms. In practice, this can only be the case if

laboratories and reagent/analyser manufacturers pay close attention to the variables inherent in INR/ISI assignment. Crucial to accurate INR results is effective local system calibration for each batch of thromboplastin.

The increase in patients requiring anticoagulation has lead to different models of patient management. Traditional hospital-based clinics persist although dosing may be done by suitably trained nurses, pharmacists or scientists as well as medical staff. General practitioners and local pharmacists are increasingly being used in ambulatory based clinics for stable, uncomplicated patients. The advent of point-of-care testing devices for PT/INR determination now allows selected patients to self-test and even self-dose.

Even with effective INR analysis and expert dosing, warfarin is associated with some adverse effects, such as haemorrhage, osteoporosis and purple toe syndrome. Patients with apparent warfarin resistance should be evaluated for compliance, dietary habits and influence of polypharmacy. Genuine warfarin resistance can occur from increased metabolic clearance, decreased absorption or abnormal pharmacodynamics. Heritable warfarin resistance has been described associated with genes coding for components of the cytochrome P450 enzyme system and vitamin K epoxide reductase subunit 1.

When used appropriately and monitored in an informed manner, warfarin can be a cost-effective anticoagulant drug and provide positive patient satisfaction and clinical outcomes.

Chapter 12 - There is international consensus that the current approach to medicines regulation, based on pre-market testing supported by voluntary adverse event reporting, is no longer adequate to ensure optimal use of medicines or to protect public safety. An expansion of this system is required that includes *ongoing* monitoring of medicines conducted in the market-place of community use - for benefits as well as for the systematic evaluation of adverse effects. *All available evidence* on the performance of medicines should be utilised to achieve this. In many countries a large amount of information about medicines use is already captured in administrative collections. These data can provide a significant contribution by enabling detailed insights into the individual experiences of large numbers of patients.

There are a number of reasons why the current approach to medicines evaluation cannot fully reveal the consequences of medicines use in the real-world. Important factors include the brevity of pre-market clinical trials - most of these trials are conducted for a period of no more than 12 months and reveal only limited surrogate end-points for clinical use of medicines. In addition, statistical power to detect uncommon outcomes is low, subject selection is biased and drug interactions are not examined. The result is that risk is underestimated and benefits may be overestimated compared to actual use in the community. The traditional regulatory approach has relied on a 'safety net' of post-market voluntary adverse event reporting; however reporting rates are low, the system is unlikely to detect rare or unexpected events and likely to overlook common events with well known causes. Benefits, or further evidence of efficacy, are not collated or examined at all in any systematic way.

Electronic health services data have been collected by Australian jurisdictions for many years. The quality and coverage of these data, when confidentially linked, exceeds that of many comparable collections overseas, especially for prescription medicines. Information technology has advanced to a level of sophistication that now allows rapid collation and analysis of these large data sets. With recent progress in developing a national data linkage infrastructure under the National Collaborative Research Infrastructure Strategy, Australia is

in a position to provide a model for other countries in developing a Medicines Monitoring System based on this resource.

Chapter 13 - Therapeutic drug monitoring (TDM) of antiepileptic drugs (AEDs) has made it possible to reveal non-compliance in patients, to study the individual variations in drug utilization occurring normally, or as a consequence of disease or otherwise altered physiologic states and for quality assurance aspects. Older AEDs, like phenytoin, carbamazepine and valproic acid, have a pronounced inter-individual variability in their pharmacokinetics and a narrow therapeutic range. For these drugs it has been common practice to adjust the dosage to achieve a serum drug concentration within a predefined "therapeutic range," representing an interval where most patients are expected to show an optimal response. However, such ranges must be interpreted with caution since many patients are optimally treated when they have serum concentrations below or above the suggested range. Now, several new AEDs (felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin and zonisamide) are available. For all AEDs, it would be more appropriate to focus on the concept of "individualized reference concentrations" rather than "therapeutic ranges", aiming at identifying the optimal concentration at which each patient shows the best response.

The pharmacokinetic variability is less pronounced for the new AEDs that are eliminated completely (gabapentin, pregabalin and vigabatrin) or mainly unchanged (levetiracetam and topiramate) through the kidneys. However, the dose-dependent absorption of gabapentin increases its pharmacokinetic variability. Comedication can affect drug concentration markedly for AEDs that are metabolized, and individual factors such as age, pregnancy, and renal function will contribute to the pharmacokinetic variability of all renally eliminated AEDs. For the new AEDs that are cleared by metabolism (felbamate, lamotrigine, oxcarbazepine, tiagabine and zonisamide) pharmacokinetic variability is just as relevant as for many of the traditional AEDs. TDM is therefore likely to be useful in many clinical settings also with the arrival of the new generation AEDs. In addition, many AEDs are now also used for non-epilepsy disorders, like bipolar disorder, neuropathic pain and migraine, with a potential benefit of TDM.

Chapter 14 - Clozapine, an atypical antipsychotic with superior efficacy in the treatment of refractory schizophrenia, can cause agranulocytosis in 1-2% of patients. Much discussion has revolved around the standardized blood monitoring regimes, routinely performed with the use of this drug, which have been advocated in the West but adopted only in some countries in the East. Recommendations are provided here that retain ethical practice and may be beneficial in avoiding legal repercussion in instances when those prescribed guidelines are not or cannot be followed, more especially applicable in countries where blood monitoring during Clozapine use is not mandatory or adhered to.

It is hereby proposed that a risk-benefit assessment in the form of a pro forma first be processed if blood sampling is refused. There must not be any compromise on the weekly blood checks for the first 18 weeks of treatment but thereafter, a regime of fortnightly checks for 6 weeks and subsequently, 4-weekly checks for a further 6 months is suggested. Finally, quarterly total and differential white blood cell (WBC) count testing could safely be carried out from a year after commencement of Clozapine therapy. However, these ideas should not be considered an alternative option but merely as a last resort measure.

Chapter 15 - Despite the rise of literature in the field, limited number of nanomedicines have reached the market. There is, therefore, an urgent need for new ideas able to impact on

the way of delivering active agents to diseases. The combination of nanotechnologies with very important pharmacological activity and imaging capabilities (i.e., "nanotheragnostics") represents the "grail" of the scientists in the pharmaceutical world. In this context, the authors describe in this chapter a new concept of nanomedicine with high drug loading, integrating a theragnostic approach which combines dual disease targeting and imaging functionalities.

Chapter 16 - Polymers are one of the most important materials in the design of controlled drug delivery systems due to their versatility, biocompatibility, biodegradability, drug loading properties and possibility of targeted drug release. In this chapter, the most basic parameters determining drug loading to a given polymeric carrier are discussed (mainly the type of polymer, the pH and the drug concentration). Two mechanisms of drug incorporation are widely followed: absorption or entrapment in the polymeric network, and surface adsorption. Several characterization methods have been proposed for the investigation of drug loading: qualitative characterizations, e.g., electrophoresis, and quantitative determinations, e.g., UV-Vis spectrophotometry, high-performance liquid chromatography (HPLC) or Fourier transform infrared spectroscopy (FTIR). The control of the formulation conditions is also very important in order to assure the synthesis of well-formed particles, avoiding the formation of macroaggregates or solids unsuitable for the parenteral route. Finally, the factors determining the preparation of a drug carrier with controlled drug release properties are also discussed (principally, the mechanism of drug incorporation, the amount of drug loaded and the type of polymer).

CONTENTS

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Chapter 1

DRUG TARGETING STRATEGIES IN CANCER TREATMENT

José L. Arias*
Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy,
University of Granada, Campus Universitario de Cartuja s/n, 18071 Granada, Spain.

ABSTRACT

Current anti-cancer drugs have little or no specificity for tumor cells, resulting in low concentrations at the cancer region (inefficacy), systemic toxicity and severe side effects. In order to beat this challenge, the development of anti-tumor drug delivery strategies has been proposed to improve drug localization at the tumor region and, therefore, to increase the anti-cancer efficacy, while reducing the systemic side effects. In this chapter, the possibilities of very promising strategies for controlling the biodistribution profiles of chemotherapy agents are investigated: passive targeting (through the enhanced permeability and retention effect) and active targeting (including ligand-mediated delivery and stimuli-sensitive carriers) strategies, involving the use of drug carriers.

I. INTRODUCTION

Even though several multiple chemotherapeutic regimens have been proposed to improve clinical success, cancer treatment failure is frequently encountered even in those cancers that are more sensitive to chemotherapy agents. In other to overcome this poor anti-tumor efficacy, the association of chemotherapy drugs with colloidal delivery systems in cancer treatment has been proposed to improve their efficacy and to reduce the toxicity. These associations should result in a specific accumulation in the tumor region and in a prolongation of the exposure of the cancer cells to these agents. Another benefit of drug localization in the targeted region is the improvement of its pharmacokinetic profile. Furthermore, a reduction in

* Corresponding author: E-mail: jlarias@ugr.es; Tel.: (+34) 958 24 39 00; Fax: (+34) 958 24 89 58