



HANDBOOK OF ANALYTICAL SEPARATIONS

SERIES EDITOR: ROGER M. SMITH

VOLUME 5

**DRUG MONITORING AND
CLINICAL CHEMISTRY**

**EDITED BY
GEORG HEMPEL**

Drug Monitoring and Clinical Chemistry

Edited by

GEORG HEMPEL

*Institut für Pharmazeutische und Medizinische Chemie,
Universität Münster, Germany*



2004

ELSEVIER

Amsterdam – Boston – Heidelberg – London – New York – Oxford
Paris – San Diego – San Francisco – Singapore – Sydney – Tokyo

ELSEVIER SCIENCE B.V.
Sara Burgerhartstraat 25
P.O. Box 211, 1000 AE
Amsterdam, The Netherlands

ELSEVIER Inc.
525 B Street, Suite 1900
San Diego, CA 92101-4495
USA

ELSEVIER Ltd
The Boulevard, Langford Lane
Kidlington, Oxford, OX5 1GB
UK

ELSEVIER Ltd
84 Theobalds Road
London WC1X 8RR
UK

© 2004 Elsevier B.V. All rights reserved.

This work is protected under copyright by Elsevier B.V., and the following terms and conditions apply to its use:

Photocopying

Single photocopies of single chapters may be made for personal use as allowed by national copyright laws. Permission of the Publisher and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale, and all forms of document delivery. Special rates are available for educational institutions that wish to make photocopies for non-profit educational classroom use.

Permissions may be sought directly from Elsevier's Rights Department in Oxford, UK: phone: (+44) 1865 843830, fax: (+44) 1865 853333, e-mail: permissions@elsevier.com. Requests may also be completed on-line via the Elsevier homepage (<http://www.elsevier.com/locate/permissions>).

In the USA, users may clear permissions and make payments through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, USA: phone: (+1) (978) 7508400, fax: (+1) (978) 7504744, and in the UK through the Copyright Licensing Agency Rapid Clearance Service (CLARCS), 90 Tottenham Court Road, London W1P 0LP, UK: phone: (+44) 207 631 5555; fax: (+44) 207 631 5500. Other countries may have a local reprographic rights agency for payments.

Derivative Works

Tables of contents may be reproduced for internal circulation, but permission of Elsevier Science is required for external resale or distribution of such material. Permission of the Publisher is required for all other derivative works, including compilations and translations.

Electronic Storage or Usage

Permission of the Publisher is required to store or use electronically any material contained in this work, including any chapter or part of a chapter.

Except as outlined above, no part of this work may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the Publisher.

Address permissions requests to: Elsevier's Science & Technology Rights Department, at the phone, fax and e-mail addresses noted above.

Notice

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made.

First edition 2004

Library of Congress Cataloging in Publication Data

A catalog record is available from the Library of Congress.

British Library Cataloguing in Publication Data

A catalogue record is available from the British Library.

ISBN: 0-444-50972-0

ISSN: 1567-7192

∞ The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).
Printed in The Netherlands.

Drug Monitoring and Clinical Chemistry

HANDBOOK OF ANALYTICAL SEPARATIONS

Series Editor: ROGER M. SMITH

In this series:

Vol. 1: Separation Methods in Drug Synthesis and Purification

Edited by K. Valkó

Vol. 2: Forensic Science

Edited by M.J. Bogusz

Vol. 3: Environmental Analysis

Edited by W. Kleiböhmer

Vol. 4: Bioanalytical Separations

Edited by I.D. Wilson

Vol. 5: Drug Monitoring and Clinical Chemistry

Edited by G. Hempel

Preface

Drug monitoring has been practised for about 30 years now. Initially, the concept was limited due to methodological problems in analysing low concentrations of drugs in biological fluids. In earlier times, only thin-layer chromatography and spectroscopic methods were available for analysing complex matrices. Now, as can be seen from the first chapters of this book, the methodology has clearly improved and a number of alternative methods are available for most analytical problems. Today, almost all drugs can be separated from complex matrices like human blood or other biological material and determined in very low concentrations. In the future, the availability of mass spectrometric detectors at a reasonable price will enable the analyst to solve more analytical problems in the clinic.

Selection of a suitable method for a given analytical problem is often not only made based on the question which method is scientifically most appropriate. The personal expertise of the analyst also plays an important role because some experience is still required for running chromatographic or electrophoretic methods when analysing drugs in biological fluids. Furthermore, the limited availability of capillary electrophoresis, which is one of the most suitable methods for drug analysis when not too low concentrations are present, means it is not used as often as chromatographic or immunochemical methods.

With most of the analytical problems solved, the question that arises is: are the measured concentrations of the drug in the biological fluid clinically relevant? Clinical relevance of the measured concentrations implies that there is a clear relationship between the concentration and the effect of the drug. If this is the case, the next step is to show that dose individualisation based on drug concentration measurements can standardise the individual's exposure to the drug. Even more important, one has to clarify if there is a clinical endpoint which can be positively influenced by individualising drug therapy.

For the therapeutic areas covered in this book, it has been shown that patients do benefit from therapeutic drug monitoring (TDM), although this is not the case in all therapeutic areas. However, with the limited financial resources in the clinic, even in the developed countries, one has to show that TDM is also cost-effective and the efforts in

the laboratory result in reductions in mortality, severe side-effects that would lead to longer hospitalisation and/or prolonged pharmacotherapy.

Another concept for dose individualisation, which was introduced in the late 1980s, is the area of pharmacogenetics. Pharmacogenetic methods have been shown to be an important tool for identifying patients at risk of experiencing severe toxicity or underdosing. However, there are still concerns if pharmacogenetics is effective from a pharmaco-economic point of view. In the future, methods for genotyping based on chip technology will become cheaper and easier to handle, so pharmacogenetics definitely has the potential to be a routine tool to optimise pharmacotherapy in the clinic. However, even when many more genes responsible for drug metabolism or distribution have been identified, this approach will not completely replace drug monitoring in the future.

Finally, I would like to thank all the contributors to this book for their efforts. Hopefully, the reader will find useful information for setting up or improving TDM in the clinic, for teaching purposes and to become up-to-date on recent developments in this field. I would like to thank Prof. Boos and all other colleagues from the department of Paediatric Oncology (University Children's Hospital Manchester) for the excellent collaboration and want to dedicate the book to my teacher Gottfried Blaschke, a great analyst, with many thanks for his support over the years.

Georg Hempel

Contents

<i>Preface</i>	v
--------------------------	---

Chapter 1. Sample preparation for the analysis of drugs in biological fluids

Yoshihiro Saito, Makiko Hayashida and Kiyokatsu Jinno.	1
1.1 Introduction	1
1.2 Conventional sample preparation for biological samples	2
1.2.1 Methods of protein removal	2
1.2.2 Liquid-liquid extraction (LLE)	3
1.2.3 Solid-phase extraction (SPE)	3
1.3 Microextraction methods for biological analyses	7
1.3.1 Solid-phase microextraction (SPME).	7
1.3.2 In-tube solid-phase microextraction (In-tube SPME)	8
1.3.3 Other novel miniaturized extraction techniques	9
1.4 Future prospects in biological sample preparation methods	10
1.5 Acknowledgements	11
1.6 References.	11

Chapter 2. Chromatographic methods for the analysis of drugs in biological fluids

Hassan Y. Aboul-Enein, Mohamed M. Hefnawy and Kenichiro Nakashima	15
2.1 Introduction	15
Part I. Chromatographic methods of analysis of drugs in biological fluids	16
2.2 HPLC	16
2.2.1 UV detection	16
2.2.2 FL detection.	34
2.3 LC/MS	39
2.3.1 Single MS detection system	39
2.3.2 Tandem MS detection system.	40

2.4	GC.	42
2.5	GC/MS	42
2.5.1	Non-derivatization method	43
2.5.2	Derivatization method	44
2.6	Other methods.	47
Part II. Chromatographic methods for the analysis of chiral drugs in biological fluids		49
2.7	Introduction	49
2.8	Pirkle concept chiral columns	56
2.9	Cellulose-derivative chiral columns	56
2.10	Amylose-derivative chiral columns.	63
2.11	Cyclodextrin-derivative chiral columns.	64
2.12	Cyclodextrin-derivative chiral mobile phase additives	64
2.13	Protein chiral columns	65
2.13.1	AGP column	65
2.13.2	HSA column.	66
2.13.3	Ovomucoid column	66
2.14	Macrocyclic antibiotic chiral columns.	66
2.14.1	Vancomycin column.	66
2.14.2	Teicoplanin column	66
2.14.3	Ristocetin A column.	67
2.15	GC.	67
2.16	Indirect chiral chromatographic methods.	67
2.17	Other methods.	68
2.18	List of abbreviations	68
2.19	References.	69

Chapter 3. Capillary electrophoresis for the determination of drugs in biological fluids

	Zakariya K. Shihabi	77
3.1	Introduction	78
3.2	CE, HPLC and immunoassays in drug analysis	78
3.3	Instrumentation and detection	79
3.4	Modes of CE in drug analysis and detection	80
3.4.1	Capillary zone electrophoresis (CZE) (Free solution CE)	80
3.4.2	Micellar electrokinetic capillary chromatography (MECC)	80
3.4.3	Chiral separation	80
3.4.4	Non-aqueous CE (NACE)	80
3.5	Buffers	81
3.6	Sample size and injection.	81
3.7	Sample preparation in CE.	81
3.7.1	Off-column concentration.	82
3.7.1.1	Solid-phase microextraction (SPME).	82
3.7.1.2	Molecular imprints	82
3.7.1.3	Membrane based techniques	83

3.7.1.4	Immunoaffinity solid-phase extraction	83
3.7.1.5	Homogeneous liquid-liquid extraction	83
3.7.2	Online concentration	83
3.7.2.1	Solid-phase extraction	83
3.7.2.2	Stacking	83
3.7.2.2.1	Methods for stacking for capillary zone electrophoresis	84
3.7.2.2.1.1	Isotachopheresis (ITP) and transient-ITP	84
3.7.2.2.1.2	(Pseudo-transient-ITP)	84
3.7.2.2.1.3	High-field stacking	84
3.7.2.2.2	Stacking in MECC	85
3.8	Precision	85
3.9	CE and basic information for drugs	85
3.9.1	Chiral separation	86
3.9.2	Acid dissociation constant (pKa)	86
3.9.3	Predicting drug-membrane interactions	87
3.9.4	Free and bound drugs	87
3.10	Selected applications of drugs analyzed by CE	88
3.11	References.	92

Chapter 4. Immunoassays for therapeutic drug monitoring and clinical toxicology

	William Clarke	95
4.1	Introduction	95
4.2	Immunoassays.	98
4.2.1	Homogenous vs. heterogeneous immunoassays	98
4.2.2	Competitive binding immunoassays	99
4.2.3	Non-competitive (immunometric) immunoassays	100
4.2.4	Immunoassay labels.	101
4.2.4.1	Fluorescence	101
4.2.4.2	Enzymes.	102
4.2.4.3	Chemiluminescence.	106
4.2.5	Immunoassay interferences	107
4.2.6	Point-of-care immunoassays	109
4.3	References.	110

Chapter 5. Validation of bioanalytical methods

	S. Berthier	113
5.1	Introduction	113
5.2	Requirements for bioanalytical methods	113
5.3	Pre-study validation.	114
5.3.1	Scope	114
5.3.2	Validation procedure for a new analytical method	114
5.3.2.1	General information.	114
5.3.2.2	Reference standard(s).	115

5.3.2.3	Calibration curve	115
5.3.2.4	Quality control samples.	116
5.3.2.5	Sensitivity	117
5.3.2.6	Absolute extraction recovery and matrix effect	117
5.3.2.7	Selectivity	117
5.3.2.8	Stability	118
5.3.2.9	Dilution	119
5.3.3	Validation procedure for an existing method	119
5.3.3.1	Method transfer between laboratories and/or instruments	119
5.3.3.2	Modifications to an existing assay	119
5.3.3.3	Application to different species or matrices	120
5.3.4	Documentation and archiving.	120
5.4	Within study validation	120
5.4.1	Scope	120
5.4.2	Procedure	120
5.4.2.1	Daily calibration curve	121
5.4.2.1.1	Chromatographic assays	121
5.4.2.1.2	Binding assays	121
5.4.2.1.3	Acceptance criteria	121
5.4.2.1.4	LLOQ and ULOQ.	121
5.4.2.2	Quality control samples.	122
5.4.2.3	Criteria for samples repeat analysis	122
5.4.3	Documentation	124
5.5	Definitions.	125
5.6	Abbreviations	127
5.7	References.	128

Chapter 6. Pharmacokinetic methods for analysis, interpretation, and management of TDM data, and for individualizing drug dosage regimens optimally

Roger Jelliffe, Alan Schumitzky, David Bayard,

Michael Van Guilder, Robert Leary, Andreas Botmen,

Ashutosh Gandhi, Pascal Maire, Xavier Barbaut,

Nathalie Bleyzac, Irina Bondareva and Michael Neely

129

6.1	Introduction and overview	129
6.1.1	Problems with “Therapeutic Ranges”	130
6.1.2	Setting specific target goals based on need.	131
6.2	The need for models	132
6.3	Maximum a posteriori probability (MAP) Bayesian individualization of drug dosage regimens.	133
6.4	Analyzing assay and environmental sources of error.	136
6.4.1	Overview	136
6.4.2	Determining the assay error polynomial	136
6.4.3	No lower limit of quantification for pharmacokinetic work and	

	TDM	136
6.4.4	The SD is what is important, not the CV	138
6.4.5	Determining the remaining environmental error	138
6.5	Examples of MAP Bayesian target-oriented, model-based, approaches to patient care	139
6.5.1	Gentamicin therapy	139
6.5.2	Timing the aminoglycoside dose and the dialysis	141
6.6	Other studies of outcome and cost of TDM	141
6.6.1	Gentamicin therapy	141
6.6.2	Amikacin therapy	142
6.6.3	Vancomycin therapy	143
6.6.4	Digoxin therapy	143
6.6.5	Lidocaine therapy	145
6.6.6	Busulfan therapy	146
6.7	Why we really monitor serum concentrations: for clinician-managed, model-based, target-oriented individualized drug therapy	146
6.8	Optimal TDM monitoring strategies	147
6.8.1	More general comments	148
6.9	Special cases: entering initial conditions – changing population models during the fitting procedure	150
6.9.1	An aminoglycoside patient with a sudden change in clinical status and volume of distribution	151
6.10	Linked pharmacodynamic models: bacterial growth and kill	152
6.10.1	General considerations	152
6.11	Other linked pharmacodynamic models: aminoglycoside nephrotoxicity and ototoxicity	155
6.12	Limitations of current map bayesian adaptive control	157
6.13	Overcoming the separation principle: “multiple model” design of maximally precise drug dosage regimens	158
6.13.1	Obtaining “multiple model” Bayesian posterior joint parameter distributions	160
6.13.2	Other bayesian approaches	161
6.13.3	MM clinical application	164
6.13.4	Analyzing the changing tobramycin patient with MM and IMM sequential Bayesian methods: implementation into clinical software	165
6.14	The future of individualized drug therapy	165
6.15	Acknowledgments	166
6.16	References.	166

Chapter 7. Dose and therapy individualisation in cancer chemotherapy

	Georg Hempel	169
7.1	Introduction	169
7.2	Concepts of dose finding in oncology	170
7.2.1	Dosing based on patient characteristics	171

7.2.2	Dosing based on pharmacodynamic parameters	172
7.2.3	Therapeutic drug monitoring of anticancer drugs	173
7.2.3.1	Analytical aspects	174
7.2.3.2	Mercaptopurine	175
7.2.3.3	Methotrexate	177
7.2.3.4	Etoposide/Teniposide	180
7.2.3.5	Carboplatin	182
7.2.3.6	Busulfan	183
7.3	5-Fluorouracil (5-FU)	186
7.4	In-vitro-cytotoxicity as a tool for therapy individualisation	186
7.5	Dosing based surrogate markers	187
7.6	Conclusions	187
7.7	References	188

Chapter 8. Rationale and utility of therapeutic drug monitoring for the optimization of antibiotic therapy

	Christine T. Ong and David P. Nicolau	195
8.1	Introduction	195
8.2	Vancomycin	196
8.2.1	Background	196
8.2.2	Pharmacology	196
8.2.3	Drug concentrations and clinical efficacy	196
8.2.3.1	Concentrations and toxicity	197
8.2.4	Monitoring serum drug concentration	198
8.3	Aminoglycosides	199
8.3.1	Background	199
8.3.2	Pharmacology	200
8.3.3	Intermittent versus once-daily aminoglycosides	200
8.3.4	Side-effects	202
8.3.5	Dosing strategies	203
8.4	Antitubercular agents	205
8.4.1	Background	205
8.4.2	Pharmacology of antimycobacterial agents	206
8.4.3	Serum concentrations and clinical efficacy	206
8.4.4	Toxicity	208
8.4.5	Monitoring of drug concentrations	209
8.4.6	Dosing adjustments	209
8.4.7	Drug interactions	210
8.5	Antiretroviral therapeutic drug monitoring (ATDM)	210
8.5.1	Introduction	210
8.5.2	Serum concentrations and efficacy	210
8.5.3	Serum concentration and clinical outcomes	211
8.5.4	Future of ATDM	211

8.6	Conclusion	212
8.7	References.	212

Chapter 9. Therapeutic drug monitoring of antiepileptic drugs

	Svein I. Johannessen	221
	Abstract.	221
9.1	Introduction	221
9.1.1	What to measure?	222
9.1.1.1	Total versus free drug serum levels.	222
9.1.1.2	Serum levels of drug metabolites.	223
9.1.2	Analytical aspects.	223
9.1.2.1	Comparison of methods.	224
9.1.2.2	Quality control	224
9.1.3	Blood sampling time	224
9.1.4	The therapeutic range.	225
9.2	Established antiepileptic drugs	226
9.2.1	Phenobarbital	226
9.2.1.1	Mechanism of action	226
9.2.1.2	Pharmacokinetics and drug interactions	227
9.2.1.3	Clinical use and side effects	227
9.2.1.4	Serum levels and therapeutic effect.	228
9.2.1.5	Analytical methods	228
9.2.2	Phenytoin	228
9.2.2.1	Mechanism of action	228
9.2.2.2	Pharmacokinetics and drug interactions	228
9.2.2.3	Clinical use and side effects	229
9.2.2.4	Serum levels and therapeutic effect.	229
9.2.2.5	Analytical methods	229
9.2.3	Primidone	229
9.2.3.1	Mechanism of action	229
9.2.3.2	Pharmacokinetics and drug interactions	230
9.2.3.3	Clinical use and side effects	230
9.2.3.4	Serum levels and therapeutic effect.	230
9.2.3.5	Analytical methods	231
9.2.4	Carbamazepine	231
9.2.4.1	Mechanism of action	231
9.2.4.2	Pharmacokinetics and drug interactions	231
9.2.4.3	Clinical use and side effects	232
9.2.4.4	Serum levels and therapeutic effect.	232
9.2.4.5	Analytical methods	232
9.2.5	Valproate	232
9.2.5.1	Mechanism of action	232
9.2.5.2	Pharmacokinetics and drug interactions	232
9.2.5.3	Clinical use and side effects	233

	9.2.5.4	Serum levels and therapeutic effect.	233
	9.2.5.5	Analytical methods	233
9.2.6		Ethosuximide	233
	9.2.6.1	Mechanism of action	233
	9.2.6.2	Pharmacokinetics and drug interactions	234
	9.2.6.3	Clinical use and side effects	234
	9.2.6.4	Serum levels and therapeutic effect.	235
	9.2.6.5	Analytical methods	235
9.2.7		Clonazepam	235
	9.2.7.1	Mechanism of action	235
	9.2.7.2	Pharmacokinetics and drug interactions	235
	9.2.7.3	Clinical use and side effects	236
	9.2.7.4	Serum levels and therapeutic effect.	236
	9.2.7.5	Analytical methods	236
9.2.8		Clobazam	236
	9.2.8.1	Mechanism of action	236
	9.2.8.2	Pharmacokinetics and drug interactions	237
	9.2.8.3	Clinical use and side effects	237
	9.2.8.4	Serum levels and therapeutic effect.	237
	9.2.8.5	Analytical methods	237
9.3		Newer antiepileptic drugs.	237
9.3.1		Oxcarbazepine	237
	9.3.1.1	Mechanism of action	237
	9.3.1.2	Pharmacokinetics and drug interactions	238
	9.3.1.3	Clinical use and side effects	238
	9.3.1.4	Serum levels and therapeutic effect.	238
	9.3.1.5	Analytical methods	239
9.3.2		Vigabatrin	239
	9.3.2.1	Mechanism of action	239
	9.3.2.2	Pharmacokinetics and drug interactions	239
	9.3.2.3	Clinical use and side effects	239
	9.3.2.4	Serum levels and therapeutic effect.	240
	9.3.2.5	Analytical methods	240
9.3.3		Lamotrigine	240
	9.3.3.1	Mechanism of action	240
	9.3.3.2	Pharmacokinetics and drug interactions	240
	9.3.3.3	Clinical use and side effects	241
	9.3.3.4	Serum levels and therapeutic effect.	241
	9.3.3.5	Analytical methods	241
9.3.4		Gabapentin	241
	9.3.4.1	Mechanism of action	241
	9.3.4.2	Pharmacokinetics and drug interactions	242
	9.3.4.3	Clinical use and side effects	242
	9.3.4.4	Serum levels and therapeutic effect.	242
	9.3.4.5	Analytical methods	242

9.3.5	Topiramate	243
9.3.5.1	Mechanism of action	243
9.3.5.2	Pharmacokinetics and drug interactions	243
9.3.5.3	Clinical use and side effects	243
9.3.5.4	Serum levels and therapeutic effect.	243
9.3.5.5	Analytical methods	244
9.3.6	Felbamate	244
9.3.6.1	Mechanism of action	244
9.3.6.2	Pharmacokinetics and drug interactions	244
9.3.6.3	Clinical use and side effects	245
9.3.6.4	Serum levels and therapeutic effect.	245
9.3.6.5	Analytical methods	245
9.3.7	Tiagabine	245
9.3.7.1	Mechanism of action	245
9.3.7.2	Pharmacokinetics and drug interactions	245
9.3.7.3	Clinical use and side effects	246
9.3.7.4	Serum levels and therapeutic effect.	246
9.3.7.5	Analytical methods	246
9.3.8	Levetiracetam	246
9.3.8.1	Mechanism of action	246
9.3.8.2	Pharmacokinetics and drug interactions	246
9.3.8.3	Clinical use and side effects	247
9.3.8.4	Serum levels and therapeutic effect.	247
9.3.8.5	Analytical methods	247
9.3.9	Zonisamide	247
9.3.9.1	Mechanism of action	247
9.3.9.2	Pharmacokinetics and drug interactions	247
9.3.9.3	Clinical use and side effects	248
9.3.9.4	Serum levels and therapeutic effect.	248
9.3.9.5	Analytical methods	248
9.4	References.	248

Chapter 10. Therapeutic drug monitoring of antidepressant and antipsychotic drugs

	Philip B. Mitchell	255
10.1	Introduction	255
10.2	Rationales for use of therapeutic drug monitoring of antidepressant and antipsychotic drugs	255
10.2.1	Therapeutic ranges.	255
10.2.2	Toxicity	255
	10.2.2.1 Monotherapy and genetic polymorphisms	256
	10.2.2.2 Combined therapies – Interactions and genetic polymorphisms	257
10.2.3	Subtherapeutic concentrations.	257
10.2.4	Overdose.	257

10.3	Antidepressants	258
10.3.1	Tricyclic antidepressants (TCAs)	258
10.3.1.1	Clinical issues	258
10.3.1.2	Assay methods	258
10.3.1.3	Sampling times and intervals.	259
10.3.1.4	Therapeutic ranges	259
10.3.1.5	Relationship between genotype and serum concentrations	260
10.3.1.6	Interactions and other determinants of plasma concentrations	261
10.3.2	Selective serotonin reuptake inhibitors (SSRIs).	262
10.3.2.1	Clinical issues and therapeutic ranges	262
10.3.2.2	Assay methods	263
10.3.2.3	Sampling times and intervals.	263
10.3.2.4	Determinants of plasma concentrations	263
10.3.3	Reboxetine.	263
10.3.3.1	Clinical issues	263
10.3.3.2	Assay methods	263
10.3.3.3	Therapeutic levels	263
10.3.3.4	Determinants of plasma concentrations	264
10.3.4	Mirtazapine	264
10.3.5	Nefazodone/trazodone	264
10.3.6	Venlafaxine	264
10.4	Antipsychotics	265
10.4.1	Typical antipsychotics	265
10.4.1.1	Assay methods	265
10.4.1.2	Therapeutic ranges	265
10.4.1.3	Relationships between genotype and serum concentrations	265
10.4.1.4	Interactions and other determinants of serum concentrations	266
10.4.2	Atypical antipsychotics	266
10.4.2.1	Assay methods	266
10.4.2.2	Therapeutic ranges	266
10.4.2.3	Relationship between genotype and serum concentrations	267
10.4.2.4	Interactions and other determinants of serum concentrations	267
10.4.2.5	Overdose	268
10.5	Lithium	268
10.6	Conclusion	268
10.7	References.	269