## Prug level Monitoring

Analytical Techniques, Metabolism, and Pharmacokinetics

Wolfgang Sadée and Geertruida C.M. Beelen

## DRUG LEVEL MONITORING

Analytical Techniques, Metabolism, and Pharmacokinetics

Wolfgang Sadée Geertruida C. M. Beelen

University of California San Francisco, California

A Wiley-Interscience Publication

JOHN WILEY & SONS

New York • Chichester • Brisbane • Toronto

# Metabolism. Pharmacokinetics

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Library of Congress Cataloging in Publication Data

Sadée, Wolfgang, 1942-Drug Level Monitoring

"A Wiley-Interscience publication."

Includes index.

1. Drugs-Analysis. 2. Drug metabolism.

3. Pharmacokinetics. I. Beelen, Geertruida C. M., 1946- joint author. II. Title. [DNLM:

1. Drug therapy. 2. Monitoring, Physiologic drug-Analysis. QV25 W859d]

RS189.S15 615.7 79-22652 9 Bone joe falmi - yeli W. A. ISBN 0-471-04881-X

Printed in the United States of America New York . Chichester . Brisbar 1 2 6 4 5 6 7 8 9 10

## PREFACE

Drug level monitoring represents an important aspect of pharmacologic research. Moreover, the value of drug serum concentrations in optimizing individual drug dosages has led to therapeutic drug level monitoring as a standard clinical practice for many important drugs. This book demonstrates how the principles of drug analysis and drug disposition are combined in drug level monitoring. It serves as a guide to the analytical techniques applicable to drug assays in biological samples, and as a reference source for metabolic and pharmacokinetic data, and is addressed to the analytical and clinical chemist, to the health-care professional specialized in drug therapy—for example the clinical pharmacologist and clinical pharmacist—and to researchers in all areas of pharmacology.

The first four chapters form a general summary of the principles of drug metabolism, pharmacokinetics, clinical pharmacokinetics, therapeutic drug level monitoring, and analytical techniques for biological samples. The specific part, Chapter 5, reviews in detail the analysis and metabolic disposition of approximately 100 selected drugs in a series of monographs. We emphasize the drugs that are currently analyzed in clinical laboratories for therapeutic purposes. Furthermore, representative drugs have been chosen from a large variety of classes—in particular, drugs of abuse, anticancer drugs, antibiotics, cardiovascular drugs, and centrally active drugs. The pertinent literature published before May 1979 is included in the monographs and updated to November 1979 in an addendum.

Wolfgang Sadée Geertruida C. M. Beelen

### **ACKNOWLEDGMENTS**

We are indebted to the Clinical Chemistry Section at the University of California at San Francisco and to the staff of the Clinical Pharmacokinetics Laboratory, in particular to J. L. Powers, B. R. Stafford, and R. A. Marques, who assisted in the development of this laboratory. The CPL provides services in therapeutic drug level monitoring at UCSF and represents the basis for this book. Several sections and drug monographs were written by J. L. Powers, B. R. Stafford, T. Guentert, and T. L. Ding. Finally, graduate students enrolled in the elective course "Bioanalytical Theory and Techniques" taught by W. Sadée at UCSF in 1978, have contributed to many monographs, and they are mentioned appropriately.

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San Francisco, California

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## INTRODUCTION

The already classical studies on the nature and significance of drug metabolism and disposition by Axelrod, Brodie, Dost, Krüger-Thiemer, and others, conducted only a few decades ago, stimulated an enormous activity in this area. We now recognize that pharmacokinetic parameters determine to a large extent the pharmacological responses of individual patients. Moreover, differences in drug disposition account for a major share of interindividual differences in drug response. Drug doses required to achieve the same response in different patients may vary by more than one order of magnitude. It is for these reasons that drug level monitoring has assumed its present importance in drug research and therapy.

The definition of drug level monitoring also outlines the scope of this book; it is the quantitative determination of drugs and their metabolites in biological specimens and the interpretation of such data using principles of pharmacokinetics and pharmacodynamics. Drug

close chemical analogs of the selected ch

level monitoring thus incorporates the following fields:

Drug metabolism
Pharmacokinetics
Pharmacodynamics
Pathophysiology
Drug analysis
Clinical chemistry
Clinical toxicology
Clinical pharmacokinetics and therapeutic drug level monitoring

Detailed investigations on the disposition of a new drug are now required before it can be applied to human clinical trials. Pharmacologic research often utilizes drug level monitoring to study the

#### 2 Introduction

mechanism of drug action, including the contribution of metabolites to the drug effect. Furthermore, bioavailability studies depend on drug level monitoring; new drug formulations have to be tested for their bioequivalence in terms of established standard preparations. Drug level monitoring in the area of drug abuse and overdose is again based on a different set of criteria and objectives. However, the most rapid growth at present occurs in the application of drug level monitoring as a guide to optimize individual drug dosage regimens. We will refer to this area as "clinical pharmacokinetics and therapeutic drug level monitoring." Most major hospitals have established clinical chemistry sections devoted to the analysis of therapeutic drug concentrations ("Drug Level Laboratory," "Clinical Pharmacokinetics Laboratory").

We have approached the complex area of drug level monitoring by selecting approximately 100 important, representative drugs. Selection criteria were as follows: a conducted only a tew decades ago, and others, conducted only a tew decades ago, and others, conducted only a tew decades ago, and others ago, and other ago

activity in this area. We now recognize that pharmacohimente 1. Drugs that are currently measured in clinical pharmacokinetics laboratories, ab aisto ni sonereriti, revoeroM atneitag laubivibui to

2. Drugs that are representative of a class of chemical or pharmacological agents (e.g., \(\epsilon\)-aminocaproic acid, chloroquin, clofibrate, ethynylestradiol, isosorbide dinitrate, succinylcholine, warfarin).

3. Drugs that belong to the following major classes: antimicrobials, anticancer drugs, antiepileptics, cardiovascular drugs, psychotropic drugs, analgesics, and drugs of abuse. Is a part of the morning bound

book; it is the quantitative determination of druce The metabolism, pharmacokinetics, and, in more detail, the analytical assays of biological specimens are reviewed in separate monographs for these 100 drugs. In addition, many more drugs listed in the register are close chemical analogs of the selected drugs, and the literature cited often contains detailed information on these analogs as well. The monographs evaluate the literature that is currently available and assist health-care professionals, pharmacologists, and analytical chemists to utilize drug level monitoring to its full potential.

Brief general chapters are designed to introduce the reader to the terminology and scope of pharmacokinetics, drug metabolism, and analytical techniques, while tables enumerate the information contained in the drug monographs for ready cross-referencing. Detailed discussions of the various general areas of interest can be found in the textbooks cited

Detailed investigations on the disposition of a new drug are no

### DRUG METABOLISM

Drugs are eliminated from the body either in the unchanged form, usually via renal excretion, or as metabolites. While it is generally assumed that drug metabolites are inactive and more readily excreted by the kidneys than is the parent drug, there are many examples of active or even toxic metabolites. Table I contains the therapeutically relevant metabolites of the listed drugs. Many of these drugs give rise to active or toxic metabolites that need to be considered in drug level monitoring. Major inactive metabolites are also included in Table I, since they may interfere with the drug level assay or can be utilized to indirectly determine the fate of the active species in the body. For example, the urinary excretion of the glucuronide of 4-OH-phenytoin, the major inactive product of phenytoin, can serve to differentiate between rapid metabolism and noncompliance in patients who do not respond to therapy (see phenytoin monograph).

Table I also includes the major mode of elimination of the active drug from the body, that is, renal or metabolic, which is an important parameter in clinical pharmacokinetics. Metabolic elimination means that the active species, either parent drug or active metabolite, is predominantly cleared by metabolic conversion to inactive products, regardless of whether or not these inactive metabolites are then excreted into the urine. For instance, diazepam is sequentially metabolized to the pharmacologically active N-desmethyldiazepam and oxazepam, followed by glucuronidation to the inactive oxazepam-3-O-glucuronide as the major urinary product. Thus the mode of elimination of active diazepam is by metabolism (see diazepam monograph). The predominance of the metabolic route as the major mode of elimination is striking. Many of the rather inert, lipophilic drugs would possess exceedingly long half-lives in the body were it not for the surprising capacity of mammalian species to metabolize almost any ingested chemical substance.

Table I. Summary of Pharmacokinetic and Metabolic Data on 102 Selected Drugs (For further details see individual drug monographs.)

	edt daj aze.	ne inp An e, i	stit den esa era	Plasma	* Plasm	Plasma levels	Major
Drug CS	Active	Toxic	Inactive	elimination° half-life	Therapeutic	Toxic	mode of elimination <sup>d</sup>
Acetaminophen	olites atlally an. en m-2-C miasa	Oxidized intermediates	S-conjugates (overdose)	2 hr, longer after toxic	1-10 µg/ml	$>10 \mu \mathrm{g/ml}$ for days	M
Acetazolamide	eps guer cpr cpr			doses $2(\alpha)$ and	~10 µg/ml		24
e-Aminocaproic				13 (β) hr ~1 hr	100-400 µg/ml		24
acid Aminopyrine	4-Aminoanti- pyrine	4-Formyl- aminopyrine (?), dimethyl-	Methylru- bazoic acid	2.7 hr	5 μg/ml (peak level)	AB	M
Amphetamine		nitrosamine nitros	Phenyl- acetone	7 hr, acidic urine; 20 hr, basic	10 ng/ml (peak level)		M + R
Anticonvulsants° Mephobarbital	Phenobarbital			24-45 hr	Therapeutic		M + R
Phenobarbital Primidone	Phenobarbital,	ulso inch he body, n clonica ive speci cleared		84-108  hr $12 \pm 6 \text{ hr}$	levels of phenobarbital 10-30 µg/ml Therapeutic	ÐU	M + R H + R
Ethotoin Mephenytoin	pnenyletnyr- malondiamide Phenylethyl- hydantoin			sotive or evidence or to solive or to inonitoring.	phenobarbital 15-50 µg/ml 15-40 µg/ml (sum of mephenytoin and phenylethyl.	AG	××

M		= = =	W		M		Z Z	X X	M M	M	AVA	W		M	TOTAL STREET	M	
						$10 \mu g/ml$ (hypnotics)										>5.5 µg/ml *	
10-20 µg/ml		$>100 \mu g/ml$ (as dimethadione)	40-100 µg/ml	$10-40 \mu g/ml$ (as N-desmethylmethsuximide	5-15 µg/ml Low ng/ml range	1–5 µg/ml						5-10 µg/ml	Donalist and	00 40/m	(peak levels)	1-3 µg/ml	
24 ± 12 hr		8 hr (dimethadione)	24-72 hr	2-4 hr	4 hr $2(\alpha)$ and 13–38 $(\beta)$ hr		14-42 hr	3-7 nr 93-30 hr	>8 hr		<15 min	18-65 hr	(single dose) 10-20 hr	(maintenance)	1.0-3.5 nr	20-24 hr (14-95 hr for	demoxenam)
4-OH-pheny-toin glucuronide		FOLCE - 15	Oxidative	on state				Lindanes of the	metabolites		g satiodatem				esifiedaten	Oxazepam	
		30 Sub-									Alkylating and carbamoylating	species			metabolitica		
	Ethylmethyl-	Dimethadione		N-Desmethyl- methsuximide		12 12 13 13 14 15 15 15 15 15 15 15 15 15 15 15 15 15	- yzododi	N-Desmethyl- hexobarbital			Alkylating and carbamoylating	species	Design	The second secon		N-Desmethyl-	demoxepam
Phenytoin	Paramethadione	Trimethadione	Ethosuximide	Methsuximide	Phensuximide Atropine	Barbiturates'	Amobarbital	Hexobarbital	Pentobarbital sodium Thiorentel	sodium	BCNU	Coshemezenine	Caroamacopus		Chloramphenicol	Chlordiazepoxide	

Table I. (Continued)

metabolites metabolites half-life Therapeutic Toxic ell  Many Many (?)  Benzoylecgonine acid metabolites  Many Many 2.5-6.5 hr Low ng/ml range  Many 2.5-6.5 hr Low ng/ml (in hypoglycemia)  24-36 hr (15-60 gg/ml  15-60 gg/ml  (10-150 ng/ml  (10-150 ng/ml  (10-150 ng/ml  (10-150 ng/ml  (10-150 ng/ml  (10-150 ng/ml  (11-50 gg/ml  (11-50 gg/ml  (12-6-3 hr 10-150 ng/ml  (13-60 hr (12-150 ng/ml  (13-60 hr (12-150 ng/ml  (14-15-150 ng/ml  (15-15-150 ng/ml  (15-15-150 ng/ml  (15-15-150 ng/ml  (15-15-150 ng/ml  (15-15-150 ng/ml  (15-150 ng/ml  (15-1	Optodynastucito	W-Benmerby	E	E, my man miga.	Plasma	Plasm	Plasma levels	Major
ne         N-Desethyl         3 (α) and 18 (β)         None defined           chloroquine         Many         6 hr (α), β-phase         50-300 ng/ml           chlorpcomazine, chlorpcomazine, chlorpcomazine         7-hydroxy-         10 nger.           chlorpcomazine         Clofibrinic acid         12 hr (clofi-         80-200 μg/ml           curonide         Prinic acid         (clofibrinic acid)           curonide         13-60 hr         5-50 μg/ml           clonidine         Benzoylecgonine         30-70 min         200 ng/ml           phamide         Aldophosphamide,         Benzoylecgonine         30-70 min         200 ng/ml           phasphoramide         mustard         Many         2.5-6.5 hr         10-150 ng/ml           metabolites         4 hr         (clofibrinic acid)         15-50 ng/ml           glucuronide         24-36 hr         10-1.0 μg/ml           nine         24-36 hr         15-50 ng/ml           nine         24-36 hr         15-50 ng/ml           nine         24-36 hr         (in hypoglycenia)	Drug governopeur	Active	Toxic	Inactive" metabolites	elimination, half-life	Therapeutic	Toxic	mode of elimination
N-Desethyl					(Althoughteen)			
Action	Chloroquine	N-Desethyl			$3(\alpha)$ and $18(\beta)$	None defined		M
Many   G hr (a), \( \beta \)-phase   50-300 ng/m    metabolites   possibly much   longer		chloroquine			days			
Clofibrinic acid	Chlorpromazine	Monodesmethyl-	Birsquis	Many	6 hr $(\alpha)$ , $\beta$ -phase	50-300 ng/ml		M
Clofibrinic acid   Clofibrinic		chlorpromazine,	s emeporal sopration	metabolites	possibly much			
Clofibrinic acid acid glu-   Drinic acid   Clofibrinic acid   Clofibrinic acid   Clofibrinic acid   Clofibrinic acid   Clofibrinic acid   Clofibrinic acid   Curonide   T-Amino-   T-Amin		7-hydroxy-			longer			
acid glu-  curonide  A-Hydroxy- clonidine  Aldophosphamide,  phamide  Aldophosphamide,  mustard  A.Desmethyl-  A.D	Clofibrate	Clofibrinic acid		Clofibrinic	19 hr (cloff.	80-900g/m]		>
A-Hydroxy-   Clonidine	Bogina			acid glu-	brinic acid)	(clofibrinic acid)		M
m         7-Amino-         7-Amino-         7-Amino-         7-Amino-         7-Amino-         7-Amino-         7-Amino-         7-Amino-         7-Amino-         13-60 hr         5-50 μg/ml           4-Hydroxy-         (?)         5-23 hr         ~1-2 ng/ml         ~1-2 ng/ml           phamide         Aldophosphamide,         Benzoylecgonine         30-70 min         200 ng/ml         0.0-150 ng/ml           phosphoramide         mustard         Many         2.5-6.5 hr         10-150 ng/ml         0.150 ng/ml           assone         mustard         Ahr         >>100 μg/ml         0.1-1.0 μg/ml         0.1-1.0 μg/ml           e         4 hr         24-36 hr         15-50 μg/ml         0.1-1.0 μg/ml         0.1-1.0 μg/ml           diazepam         24-36 hr         15-50 μg/ml         0.5-2 ng/ml         0.5-2 ng/ml				curonide				
2-3 hr   2-1 ng/ml	Clonazepam		7-Amino-	7-Aminoclon-	13-60 hr	5-50 µg/ml		M
4-Hydroxy- clonidine	astidy indozsilly		clonazepam	azepam				
4-Hydroxy- clonidine clonidine blant clonidine clonidine clonidine blant clonidine and methylecgo- phamide Aldophosphamide, phosphoramide mustard asone mustard  Many A-5-6.5 hr  Cow ng/ml range metabolites  e  N-Desmethyl- diazepam diazepam diazepam  1-5-50 µg/ml (in hypoglycemia) 1-6-50 µg/ml (in hypoglycemia) 1-6-23 hr  10-150 µg/ml (diagnostic) 0-1-1.0 µg/ml (in hypoglycemia) 1-6-50 µg/ml (in hypoglycemia) 1-6-50 µg/ml (in hypoglycemia) 1-6-50 µg/ml	lat/dtgdomA		(3)					
Dearcylecgonine   30-70 min   200 ng/ml   2.5-6.5 hr   2.5-6.5	Clonidine	4-Hydroxy-			5-23 hr	$\sim 1-2 \text{ ng/ml}$		M
phamide Aldophosphamide, nine 5.6-8.4 hr 10-150 ng/ml phosphoramide mustard Many 2.5-6.5 hr Low ng/ml range metabolites 4 hr (diagnostic)  N-Desmethyl- Grazepam 26-53 hr (diagnostic) 0.1-1.0 µg/ml (in hypoglycemia) 1.6-50 µg/ml (in hypoglycemia) 1.6-50 µg/ml (in hypoglycemia) 2.5-8.5 µg/ml	Cocaine			Benzovleceonine	30-70 min	200 ng/ml		×
Phosphoramide				and methylecgo-	13-28 (2) 171	(peak levels)		d d
phamide Aldophosphamide, 5.6-8.4 hr 10-150 ng/ml phosphoramide mustard asone  Many 2.5-6.5 hr Low ng/ml range metabolites 4 hr >>10-400 µg/ml (diagnostic)  Oxazepam 26-53 hr 0.1-1.0 µg/ml diazepam glucuronide 24-36 hr (in hypoglycemia) 1.6 days 0.5-2 ng/ml >2.6-8.4 hr 10-150 ng/ml (diagnostic) 0.1-1.0 µg/ml				nine				
asone Many 2.5-6.5 hr Low ng/ml range metabolites 4 hr >>100 µg/ml (diagnostic)  W-Desmethyl- Oxazepam 26-53 hr 0.1-1.0 µg/ml glucuronide 24-36 hr 15-50 µg/ml (in hypoglycemia) 1.6 days 0.5-2 ng/ml >2 ng/ml	Syclophosphamide	Aldophosphamide, phosphoramide mustard			5.6-8.4 hr	10-150 ng/ml		M
4 hr >>100 μg/ml (diagnostic)  N-Desmethyl- Oxazepam 26-53 hr 0.1-1.0 μg/ml.  diazepam 24-36 hr 15-50 μg/ml (in hypoglycemia) 1.6 days 0.5-2 ng/ml >2 ng/ml	Dexamethasone	N-Desmedby-		Many metabolites	2.5-6.5 hr	Low ng/ml range		M
N-Desmethyl- Oxazepam 26–53 hr 0.1–1.0 μg/ml.  diazepam diazepam 24–36 hr 15–50 μg/ml (in hypoglycemia) 1.6 days 0.5–2 ng/ml >2 ng/ml	Diatrizoate				4 hr	>>100 µg/ml (diagnostic)		R
16—16–50 $\mu$ g/ml (in hypoglycemia) 1.6 days 0.5–2 ng/ml $>$ 2 ng/ml	Diazepam	N-Desmethyl-diazepam		Oxazepam	26-53 hr	0.1-1.0 µg/ml.		M
$1.6 \text{ days} \qquad 0.5-2 \text{ ng/ml} \qquad >2 \text{ ng/ml}$	Diazoxide				24-36 hr	15-50 µg/ml		M + R
	Digoxin				1.6 days	(in nypogrycemia) 0.5-2 ng/ml	>2 ng/ml	R

M	M	Я	M	M		K X		100	TAT		R		Z Z	W W	M			M + R			×	TAT	". elimination"	M		
						$>$ 12 $\mu$ g/ml																		>7 µg/ml		
30 EPS (P. 7.	Low ng/ml range	in the β-phase 3-5 μg/ml	60-500 pg/ml	0.1-1 µg/ml	(slow i.v. infusions)	4-12 µg/ml	0-245 III IIII	Contract Contract	ng/ml range		0.5 µg/m	(peak levels)	2-26 µg/100 ml	(physiolog. conc.)	0.5-3 µg/ml			$\sim 10  u g/m$		0.8-1.2 mgd/1		2-9 ng/ml	(peak levels)	1.5-7 µg/ml		
	$0.3-1.5 \text{ hr } (\alpha)$	14–30 hr $(\beta)$ 4–5 hr	, L	10 min		2-4 hr	12-39 nr		1-2 hr		3-4 hr (\alpha).	$7-10 \text{ hr } (\beta)$	60 min	100	4-20 nr 2.6-11.2 hr	2,3-3:1 10		45_80 min	(fast acetyl.),	140-200 min	(slow acetyl.)	30-50 min		17 min $(\alpha)$ ,	100 min (β)	
(Diphenyl- methoxy) acetic	acid Aglycone	metabolites Aldehydes and	carboxylic acids	α-Fluoro-	$\beta$ -alanine	9//8	B.(p-Fluoro-	propionic acid	Methyltriazo-	lopninalazine			Many	metabolites	N-Deschloro-	benzoyl and	O-desmethyl	metabolites	isoniazid					'svitosrd'		
																			Acetyl-	nyarazınıe				Monoothulalvoine.	xylidide and	glycinexylidide (convulsants)
	Non-metablish parameter of the second parameter of the	DONOLUCIO		Estradiol	FUTP				Pyruvate and	β-ketoglutarate .	hydrazones				Desipramine							Isosorbide	mononitrates	(active?)	Monoetnyigiycine	ontimuted)
Diphenhydramine	Mozykino	Doxorubicin	Ethambutoi	Ethynylestradiol	D-Fluorouracii	Gentamicin	Haloperidol		Hydralazine		Strobard#aM	Hydrochloro-	thiazide	nyarocortisone	Imipramine	Indomethazin			Isoniazid			Isosorbide	dinitrate		Lidocaine	

Table I. (Continued)

	Active	Toxic	Inactived	Plasma	Plasn	Plasma levels	Major
Drug	metabolites	metabolites	metabolites	half-life	Therapeutic	Toxic	mode of elimination
Lichina				( Inter the work)	2 & 48 Mg		3.
Lysergide			2-Oxy-LSD	15-20 hr 3.5 hr	0.6-1.2 mEq/l 1-5 ng/ml	> 2 mEq/l	<b>2</b> 2
Melphalan	Monohydroxy-		merabolicas Telson V	30 min (dogs)	(peak levels) $1 \mu g/ml$		W
Meperidine	Normeperidine	Normeperidine		3.2-3.7 hr	(peak level) 0.6 µg/ml	>5 µg/ml	M
6-Mercaptopurine	Nucleotides of 6-mercaptopurine	(convulsant)	Thiouric acid				M
	6-methyl mercapto- purine, and	-0					
Methadone	Extractions in State 1979		N-Demethy- lated, cyclized metabolites	29 ± 5 hr	100-400 ng/ml		M
Methaqualone				26 hr $(\alpha)$ , 37 hr $(\beta)$ , 72 hr $(\gamma)$	2-3 µg/ml • (peak level)	, 5-30 µg/ml	W
Methotrexate		7-OH-methotrexate	te	4-24 hr		>4.5 × 10-6 M	R
Methyldopa	α-Methyldopamine, α-methylnorepine-	ď.	A-stanton d-stanton		6 µg/ml (after 1 hr; 250 mg i.v.)	for 48 hr	M
Metronidazole	attind	2-Hydroxymethyl- metronidazole, reductive metab-	Chicaronage datherape scips special sectors	6-14 hr	5 μg/ml (antimicro- bial), 100-200 μg/ml (radio-sensitizer)	. 78	W
Morphine	Normorphine, etc.	olites	Morphine- 3-glucucuronide	$2 \ln (\alpha)$	70 ng/ml (peak level) after 10 mg (s.c.)		M