Drug Level Monitoring

Analytical Techniques, Metabolism, and Pharmacokinetics

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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.

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CONTENTS

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 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

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:

1. Drugs that are currently measured in clinical pharmacokinetics laboratories.
2. Drugs that are representative of a class of chemical or pharmacological agents (e.g., ϵ-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.

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.

1

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.)

Drug	Active metabolites	Toxic metabolites	Inactive[a] metabolites	Plasma elimination[b] half-life	Plasma levels		Major mode of elimination[a]
					Therapeutic[c]	Toxic	
Acetaminophen		Oxidized intermediates	S-conjugates (overdose)	2 hr, longer after toxic doses	1–10 μg/ml	>10 μg/ml for days	M
Acetazolamide				2 (α) and 13 (β) hr	~10 μg/ml		R
ε-Aminocaproic acid				~1 hr	100–400 μg/ml		R
Aminopyrine	4-Aminoantipyrine	4-Formylaminopyrine (?), dimethylnitrosamine	Methylrubazoic acid	2.7 hr	5 μg/ml (peak level)		M
Amphetamine			Phenylacetone	7 hr, acidic urine; 20 hr, basic urine	10 ng/ml (peak level)		M + R
Anticonvulsants[e]							
Mephobarbital	Phenobarbital			24–45 hr	Therapeutic levels of phenobarbital		M + R
Phenobarbital				84–108 hr	10–30 μg/ml		M + R
Primidone	Phenobarbital, phenylethylmalondiamide			12 ± 6 hr	Therapeutic levels of phenobarbital		M + R
Ethotoin					15–50 μg/ml		M
Mephenytoin	Phenylethylhydantoin				15–40 μg/ml (sum of mephenytoin and phenylethylhydantoin		M

Phenytoin			4-OH-phenytoin glucuronide	24 ± 12 hr	10–20 μg/ml		M
Paramethadione	Ethylmethyloxazolidinedione						
Trimethadione	Dimethadione			8 hr (dimethadione)	>100 μg/ml (as dimethadione)		
Ethosuximide			Oxidative metabolites	24–72 hr	40–100 μg/ml		M
Methsuximide	*N*-Desmethylmethsuximide			2–4 hr	10–40 μg/ml (as *N*-desmethylmethsuximide		
Phensuximide				4 hr	5–15 μg/ml		
Atropine				2(α) and 13–38 (β) hr	Low ng/ml range		M
Barbiturates[f]					1–5 μg/ml	10 μg/ml (hypnotics)	
Amobarbital				14–42 hr			M
Hexobarbital	*N*-Desmethylhexobarbital			3–7 hr			M
Pentobarbital sodium			Hydroxylated metabolites	23–30 hr			M
Thiopental sodium				>8 hr			M
BCNU	Alkylating and carbamoylating species	Alkylating and carbamoylating species		<15 min			M
Carbamazepine	10,11-Epoxide			18–65 hr (single dose) 10–20 hr (maintenance)	5–10 μg/ml		M
Chloramphenicol				1.5–3.5 hr	20–40 μg/ml (peak levels)		M
Chlordiazepoxide	*N*-Desmethylchlordiazepoxide, demoxepam		Oxazepam glucuronide	20–24 hr (14–95 hr for demoxepam)	1–3 μg/ml	>5.5 μg/ml	M

Table I. (Continued)

Drug	Active metabolites	Toxic metabolites	Inactive[a] metabolites	Plasma elimination[b] half-life	Plasma levels		Major mode of elimination[d]
					Therapeutic[c]	Toxic	
Chloroquine	*N*-Desethyl chloroquine			3 (α) and 18 (β) days	None defined		M
Chlorpromazine	Monodesmethyl-chlorpromazine, 7-hydroxy-chlorpromazine		Many metabolites	6 hr (α), β-phase possibly much longer	50–300 ng/ml		M
Clofibrate	Clofibrinic acid		Clofibrinic acid glucuronide	12 hr (clofibrinic acid)	80–200 μg/ml (clofibrinic acid)		M
Clonazepam		7-Amino-clonazepam (?)	7-Aminoclonazepam	13–60 hr	5–50 μg/ml		M
Clonidine	4-Hydroxy-clonidine			5–23 hr	~1–2 ng/ml		M
Cocaine			Benzoylecgonine and methylecgonine	30–70 min	200 ng/ml (peak levels)		M
Cyclophosphamide	Aldophosphamide, phosphoramide mustard			5.6–8.4 hr	10–150 ng/ml		M
Dexamethasone			Many metabolites	2.5–6.5 hr	Low ng/ml range		M
Diatrizoate				4 hr	>>100 μg/ml (diagnostic)		R
Diazepam	*N*-Desmethyl-diazepam		Oxazepam glucuronide	26–53 hr	0.1–1.0 μg/ml		M
Diazoxide				24–36 hr	15–50 μg/ml (in hypoglycemia)		M + R
Digoxin				1.6 days	0.5–2 ng/ml	>2 ng/ml	R

Diphenhydramine			(Diphenyl-methoxy) acetic acid				M
Doxorubicin	Doxorubicinol		Aglycone metabolites	0.3–1.5 hr (α) 14–30 hr (β)	Low ng/ml range in the β-phase		M
Ethambutol			Aldehydes and carboxylic acids	4–5 hr	3–5 μg/ml		R
Ethynylestradiol	Estradiol		Glucuronides	6.5 hr	60–500 pg/ml		M
5-Fluorouracil	FdUMP FUTP		α-Fluoro-β-alanine (toxic?)	10 min	0.1–1 μg/ml (slow i.v. infusions)		M
Gentamicin				2–4 hr	4–12 μg/ml	>12 μg/ml	R
Haloperidol			β-(p-Fluoro-benzoyl)-propionic acid	12–39 hr	6–245 ng/ml		M
Hydralazine	Pyruvate and β-ketoglutarate hydrazones		Methyltriazolophthalazine	1–2 hr	ng/ml range		M
Hydrochlorothiazide				3–4 hr (α), 7–10 hr (β)	0.5 μg/ml (peak levels)		R
Hydrocortisone			Many metabolites	60 min	2–26 μg/100 ml (physiolog. conc.)		M M
Imipramine	Desipramine			4–20 hr	15–500 ng/ml		M
Indomethazin			N-Deschlorobenzoyl and O-desmethyl metabolites	2.6–11.2 hr	0.5–3 μg/ml		M
Isoniazid		Acetylhydrazine	N-Acetylisoniazid	45–80 min (fast acetyl.), 140–200 min (slow acetyl.)	~10 μg/ml		M + R
Isosorbide dinitrate	Isosorbide mononitrates (active?)			30–50 min	2–9 ng/ml (peak levels)		M
Lidocaine	Monoethylglycine xylidide	Monoethylglycine-xylidide and glycinexylidide (convulsants)		17 min (α), 100 min (β)	1.5–7 μg/ml	>7 μg/ml	M

Table I. (Continued)

Drug	Active metabolites	Toxic metabolites	Inactive[a] metabolites	Plasma elimination[b] half-life	Plasma levels		Major mode of elimination[d]
					Therapeutic[c]	Toxic	
Lithium				15–20 hr	0.6–1.2 mEq/l	>2 mEq/l	R
Lysergide			2-Oxy-LSD	3.5 hr	1–5 ng/ml (peak levels)		M
Melphalan	Monohydroxy-melphalan			30 min (dogs)	1 μg/ml (peak level)		M
Meperidine	Normeperidine	Normeperidine (convulsant)		3.2–3.7 hr	0.6 μg/ml	>5 μg/ml	M
6-Mercaptopurine	Nucleotides of 6-mercaptopurine, 6-methyl mercapto-purine, and 6-thioguanine		Thiouric acid				M
Methadone			*N*-Demethy-lated, cyclized metabolites	29 ± 5 hr	100–400 ng/ml		M
Methaqualone			Hydroxylated metabolites	26 hr (α), 37 hr (β), 72 hr (γ)	2–3 μg/ml (peak level)	5–30 μg/ml	M
Methotrexate		7-OH-methotrexate (?)		4–24 hr		>4.5×10^{-6} *M* for 48 hr	R
Methyldopa	α-Methyldopamine, α-methylnorepine-phrine				6 μg/ml (after 1 hr; 250 mg i.v.)		M
Metronidazole		2-Hydroxymethyl-metronidazole, reductive metab-olites		6–14 hr	5 μg/ml (antimicro-bial), 100–200 μg/ml (radio-sensitizer)		M
Morphine	Normorphine, etc.		Morphine-3-glucucuronide	2 hr (α)	70 ng/ml (peak level) after 10 mg (s.c.)		M