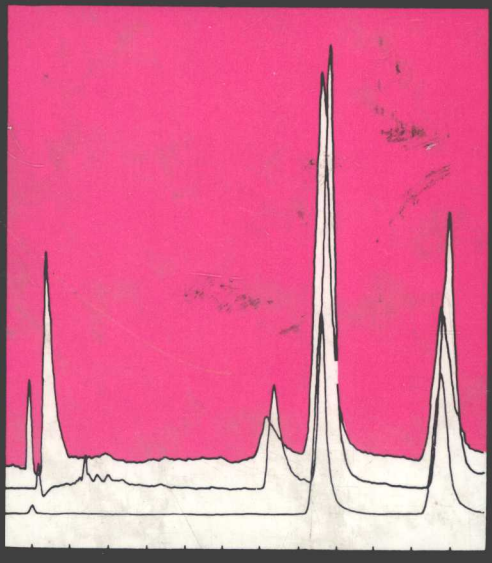
Analysis of Drugs and Metabolites by Gas Chromatography-Mass Spectrometry

Volume 5

Analgesics, Local Anesthetics, and Antibiotics



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ANALYSIS OF DRUGS AND METABOLITES BY GAS CHROMATOGRAPHY–MASS SPECTROMETRY

VOLUME 5

Analgesics, Local Anesthetics, and Antibiotics

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Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry

ANALYSIS OF DRUGS AND METABOLITES
BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY

VOLUME 1: Respiratory Gases, Volatile Anesthetics, Ethyl Alcohol, and Related Toxicological Materials

VOLUME 2: Hypnotics, Anticonvulsants, and Sedatives

VOLUME 3: Antipsychotic, Antiemetic, and Antidepressant Drugs

VOLUME 4: Central Nervous System Stimulants

VOLUME 5: Analgesics, Local Anesthetics, and Antibiotics

IN PREPARATION

VOLUME 6: Cardiovascular, Antihypertensive, Hypoglycemic, and Thyroid Related Agents

OTHER VOLUMES IN PREPARATION

Dedicated to

HELEN L. GUDZINOWICZ
a devoted and understanding wife and mother

PREFACE

In the past two decades, remarkable progress has been made in the analysis of drugs, pharmaceuticals, and related toxicological materials. In great measure, these notable advances can be attributed to technological advancements in two specific types or areas of analytical instrumentation; namely, gas chromatography and integrated gas chromatography-mass spectrometry.

Since James and Martin revealed to the scientific community their gas chromatographic technique which permitted the separation of fatty acid mixtures into their individual components, the rapid growth of gas chromatography has been very evident. This remarkable progress can be directly correlated with the improvements that we have witnessed over the years in gas chromatographic stationary phase, carrier gas, column, and temperature- and pressure-controlling technology. Furthermore, it has assumed a position of even greater analytical significance since the advent of highly specific, rapid, sensitive detection systems.

On the other hand, the integrated GC-MS analytical system is rather unique and exceptional in that it combines the mass spectrometer's unexcelled identification potential with the gas chromatograph's separation capabilities. Although the integration of GC and MS was first reported in 1957 by Holmes and Morrell, it nevertheless remained a dormant, costly, and seemingly unappreciated technique until 1970. Since then, with improved instrumentation at a more reasonable price and newly developed operating techniques, numerous publications have appeared in the literature showing its applicability to a wide variety of difficult analytical problems, thus opening up new horizons for analytical research in toxicology, biochemistry, pharmacology, forensics, medicine, etc. To be able to monitor a drug, its persistence and metabolic fate in biological fluids of man via mass fragmentography at picogram concentration levels provides the researcher with a tool of immeasurable significance.

Because much has been written over the years about the analysis of drugs and their metabolites by either or both techniques, the objectives of these volumes are several-fold: (1) to compile from existing literature in a chronological manner the various GC and/or GC-MS procedures available for the analysis of specific drugs and their metabolites, (2) to describe with as much detail as possible all procedures (qualitative and quantitative) in order that they might be reproduced faithfully in one's laboratory, and (3) to indicate, wherever possible, not only the results, precision, accuracy, and limits of detection achieved by a given procedure, but also its applicability to pharmacokinetic studies. For this reason, in addition to the text, which is well referenced in each section, many illustrations of actual applications and tables of data for each instrumental technique are included as aids to the analyst for his greater appreciation and understanding of the limitations as well as potentials ascribed to each method. As stated in the past, from an analytical chemist's point of view, it is hoped that this deliberately combined visual and factual approach will find acceptance by the reader who would otherwise rely only on his interpretation of the written word relative to some published procedure.

Without wishing to be repetitious, in retrospect it must be again stated that this volume really represents the end result of many tedious and arduous investigations by numerous eminent scientists whose research efforts have appeared in the literature throughout the world. We are indeed humbly indebted to them, and to those journals, publishers, and organizations that granted special copyright permission to the authors.

Benjamin J. Gudzinowicz
Michael J. Gudzinowicz

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OTHER VOLUMES IN PREPARATION

Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry

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Chapter 1

NARCOTICS, NARCOTIC ANTAGONISTS, AND SYNTHETIC OPIATE-LIKE DRUGS

As pointed out by Halpern [1]:

> The most common method used in managing pain is systemic administration of analgesics or other drugs. Analgesics act on the central nervous system to reduce or abolish perception of pain and interfere with the development of negative affective responses, but without producing unconsciousness. Other types of drugs are useful singly or in combination with analgesics (Table 1.1) insofar as they can decrease fear, anxiety, and apprehension; reverse depression; promote sleep; or reverse psychotic pain symptoms.

He further notes that:

> In his approach to drug selection, the physician must differentiate disorders that are primarily traumatic (a burn or broken bone), primarily pathophysiologic (infection or inflammation), or primarily psychologic (perceptive or affective disorders, neuroses, and psychoses). When a significant psychologic factor is evident or there is pain without sufficient demonstrable cause, treatment of the psychologic problem in relation to the pain becomes paramount. Affective changes induced by chronic administration of medications should not be overlooked. The patient's continuing complaints about "pain" may

be veiled requests for analgesics, sedative-hypnotics, or minor tranquilizers or for narcotic analgesics to support a drug dependence of which he may not be aware. Narcotic analgesics may partially compensate the patient; withdrawal of sedative-hypnotics, minor tranquilizers, or opiates may reveal long-standing psychoses or neurotic behavior.

The drugs discussed in this chapter that have been examined by GC and/or GC-MS techniques are the narcotic analgesics, which Goth [2] has divided into several categories: (1) natural opium alkaloids such as opium, codeine, papaverine, thebaine, laudanine, codamine, reticuline, narcotine, hydrastine, and others; (2) synthetic derivatives of opiates such as heroin, dihydromorphinone (Dilaudid), hydrocodone, methyldihydromorphinone, apomorphine, apocodeine, and others; (3) synthetic opiate-like drugs such

TABLE 1.1

Analgesics and Other Drugs for Relief of Pain[a]

Mechanisms of interference with pain	Drug type
A. Interference with central nervous system perception of pain and development of affective responses	Narcotic analgesics
B. Interference with specific chemical substance involved in pain reception periphally	Antipyretic analgesics
C. Interference with conduction of pain away from affected site	Local anesthetics
D. Reversal of specific pathophysiologic events	
1. Inflammation	Antiinflammatory agents
2. Infection	Antibiotics
3. Gout	Antihyperuricemic agents
E. Interference with anxiety, tension, or depression	1. Sedatives and hypnotics 2. Antidepressants 3. Phenothiazine tranquilizers 4. Skeletal relaxants
F. Interference with consciousness	Anesthetics

[a]Adapted from Halpern [1].

as meperidine (Pethidine), alphaprodine, methadone, levorphanol, anileridine, propoxyphene, diphenoxylate, ethoheptazine, phenylcyclidine, dipipanone, phenadoxone, methylphenidate, and others; and (4) narcotic antagonists such as N-allylnorcodeine, nalorphine, cyclazocine, pentazocine, cyclorphan, levallorphan, naloxone, naltrexone, and others. In addition to the above, other GC studies of various alkaloid species are included with those of the naturally occuring opium alkaloids, codeine and morphine. In Chapter 2, the drugs associated with categories B, C, and D of Table 1.1 will be discussed, these being essentially nonnarcotic, nonaddictive therapeutic agents.

As for the modes of therapy selected for severe, high-intensity pain other than simple analgesic medication, Halpern [1] stresses that:

> Opiates and opioids should be chosen only when nonaddictive drugs are ineffective and other forms of pain management cannot be used or are partially effective. Strong analgesics should be avoided, as too early administration may mask symptoms and make diagnosis difficult during their duration of action. Strong, or narcotic, analgesics are also associated with development of physical dependence but are considerably more effective than weaker nonaddicting agents for pain associated with burns, trauma, deep structures and musculoskeletal disorders.

The abuse liability, duration of action, and approximate adult dose of some of these analgesic drugs are listed in Table 1.2.

I. NATURAL OPIUM ALKALOIDS AND RELATED COMPOUNDS

The two main chemical classes of opium are the phenanthrene derivatives, of which morphine is the most important, and the benzoisoquinoline compounds. The predominant members of each class are listed in Table 1.3, and their structures are shown in Figure 1.1.

As described by Bowman, Rand, and West [3], "morphine and morphine-like compounds possess three characteristic chemical features: (1) a methyl group attached to the tertiary nitrogen atom, (2) several oxygen-containing groups situated at a distance of 7 to 9 Å from the tertiary nitrogen, and (3) at least one aryl nucleus attached to an asymmetric carbon which is joined by a short hydrocarbon chain to the tertiary nitrogen."

The two hydroxyl groups (the phenolic hydroxyl on carbon 3 and the alcoholic hydroxyl on carbon 6) are rather important since natural morphine derivatives can be formed by modifications at either or both of these sites

TABLE 1.2

Addictive Analgesic Drugs[a]

Compound	Approx. adult dose (mg)	Duration of action (hr)	Abuse liability
Morphine	10.0	4-5	Relatively high
Dihydromorphinone	1.5	4-5	Like morphine
Oxymorphone	1.0-1.5	4-5	Like morphine
Methyldihydromorphinone	3.0-3.5	4-5	Like morphine
Heroin	3.0	3-4	Like morphine
Nalorphine (antagonist)	10-15		None
Levorphanol	5.0	4-5	Like morphine
Phenazocine	2.0-4.0	4-5	Like morphine
Pentazocine	45.0-60.0	2-3	Substantially less than morphine
Cyclazocine	0.3	4-5	None
Meperidine	50.0-100.0	2-4	Like morphine
Anileridine	25.0-35.0	2-3	Like morphine
Piminodine	7.5-10.0	2-4	Like morphine
Alphaprodine	50.0	Very short	Like morphine
Methadone	10.0	4-5, single dose; longer in tolerant persons	Like morphine
Dipipanone	20.0-25.0	4-5	Like morphine
Dextromoramide	0.2	4-5	Like morphine

[a]Adapted from Halpern [1].

as depicted in Figure 1.2, which illustrates possible opiate metabolic pathways in man. If the 6-OH is replaced by a ketonic oxygen and the double bond adjacent to it is removed, one obtains dihydromorphinone. On the other hand, in contrast to the many useful synthetic opiate-derivatives

TABLE 1.3

Predominant Opium Alkaloids

Alkaloid class	Compound	Percent of total solids
Phenanthrene	1. Morphine	10.0
	2. Codeine	0.5
	3. Thebaine	0.2
Benzoisoquinoline	1. Noscapine	6.0
	2. Papaverine	1.0
	3. Narceine	0.3
	4. Laudanine	0.005
	5. Laudanosine	0.0008
	6. Codamine	0.003

prepared by substitutions at the hydroxyl sites, if the $-CH_3$ group on the nitrogen of morphine or levorphanol is replaced by the allyl radical $-CH_2CH=CH_2$, one obtains a nonaddicting antagonist, nalorphine or levallorphan, respectively.

The analysis of opium alkaloids and narcotic analgesics in human biological materials by gas chromatography became a reality with the advent of highly sensitive detection systems and advances in column technology. Initially, however, because most narcotics were solids with relatively high boiling points, an indirect approach was developed by Stainier and Gloesener [4], which made use of the fact that some narcotics are esters of lower alcohols. For example, after hydrolyzing cocaine and pethidine with 3.5% KOH, the resulting methyl and ethyl alcohols, respectively, were chromatographed on a 1-m Carbowax 1500 column with hydrogen as carrier gas at 70°C. In 1960, Lloyd, Fales, Highet, Vanden Heuvel, and Wildman [5] demonstrated that complex alkaloids could be separated with 2 to 3% SE-30 coated solid substrates (80-100 mesh Chromosorb W) packed in 6-ft by 4-mm-i.d. columns operated isothermally at 204°C. Using an argon ionization detector and argon (15 psi inlet pressure) as carrier gas, the retention times (in minutes) of various Papaveraceae alkaloids were codeine, 8.2; neopine, 9.1; morphine, 11.0; thebaine, 13.2; laudanosine, 21.0; papaverine, 35.3; and noscapine, 90.6 (see Vol. 4, Table 2.1). Making use of the steroid columns developed by Vanden Heuvel, Sweeley, and Horning [6], Lloyd et al. chromatographed other alkaloids, including the lupin, amaryllidaceae, indole, steroidal, quinine and tropine groups (see Vol. 4, Table 2.1).