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Review

Systematic toxicological analysis of drugs and their metabolites by gas chromatography–mass spectrometry☆

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ABSTRACT

Gas chromatographic–mass spectrometric (GC–MS) procedures for the systematic toxicological analysis of several categories of drugs relevant to clinical toxicology, forensic toxicology and doping control are reviewed. Papers from 1981 to 1991 are taken into consideration. They describe the detection of acute or chronic intoxication and the detection of drug abuse. Screening procedures are included for the following categories: barbiturates and other sedative–hypnotics, anticonvulsants, benzodiazepines, antidepressants, phenothiazine and butyrophenone neuroleptics, central stimulants (amphetamines, cocaine), hallucinogens (LSD, phencyclidine, tetrahydrocannabinol), opioid (narcotic) and other potent analgesics, non-opioid analgesics, antihistamines (histamine H_1-receptor blockers), antiparkinsonian drugs, β-blockers (β-adrenoceptor blockers), antiarrhythmics (class I and IV), diuretics, laxatives and their metabolites. Methods for confirmation of results obtained by screening procedures using immunoassay or chromatographic techniques are also included. GC–MS procedures for the simultaneous detection of several categories of drugs, the so-called "general unknown analysis", are reviewed. The toxicological question to be answered and the consequence for the choice of an adequate method, the sample preparation and the chromatography itself are discussed. The basic information about the biosample assayed, work-up, GC column, mass spectral detection mode, reference data and sensitivity of each procedure are summarized in tables, arranged according to the category of drug. Examples of typical GC MS applications are presented. Fragment ions that are suitable for mass spectral screening for particular categories of drugs and for general unknowns are tabulated.

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☆ Dedicated to Dr. med. Claudia R. Maurer, Homburg/Saar, Germany.

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LIST OF ABBREVIATIONS

AC	Acetylated
B	Blood
CI	Chemical ionization
CMP	Computer monitoring program
CU	Clean-up step
ECD	Electron-capture detection
EI	Electron-impact ionization
EN	Enzymatic cleavage of conjugates
FBC	Fluorobenzoylation by 4-fluorobenzoyl chloride
FI	Fragment ion
FSC	Fused-silica capillary
GC	Gas chromatography
GC–MS	Gas chromatography–mass spectrometry
HFB	Heptafluorobutylated
HPTLC	High-performance thin-layer chromatography
HY	Acid-hydrolysed
INN	International non-proprietary name (WHO)
IS	Internal standard
LLE	Liquid–liquid extraction
LSD	Lysergic acid diethylamide (INN: lysergide)
M	Metabolite
m/z	Mass-to-charge ratio
MAM	Monoacetylmorphine
ME	Methylated
MS	Mass spectrometry, mass spectrum
NICI	Negative-ion chemical ionization
P	Plasma
PFP	Pentafluoropropionylated
PFPRO	Pentafluoropropylated
PRO	Propylated
PS	Pure substance
RI	Retention index
RT	Retention time
SIM	Selected-ion monitoring
SPE	Solid-phase extraction
TBA	Tetrabutylammonium ion
th. conc.	Therapeutic concentrations detectable
TFA	Trifluoroacetylated
THA	Tetrahexylammonium ion
THC	Tetrahydrocannabinol
THC-COOH	11-Nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid
TM	Trade-mark
TMS	Trimethylsilylated
tox. conc.	Only toxic concentrations detectable

TPA	Tetrapentylammonium ion
TPC	Trifluoroacetylprolylation by (*S*)-(−)-trifluoroacetylprolyl chloride
u	Atomic mass unit
U	Urine

1. INTRODUCTION

Mass spectrometry (MS) was developed from 1907 to 1919 by Thomson and Aston to separate and identify isotopes. In the 1960s, MS was introduced into organic chemistry as a powerful spectroscopic method, especially for the determination of the accurate molecular mass and thereby for the calculation of the elemental composition. Additionally, it was used for the identification of unknown compounds, as the mass spectrometer reproducibly forms fragment ions which are typical for substructures of organic molecules.

In the 1970s, MS was directly coupled with chromatographic methods, especially with gas chromatography (GC). This coupling revolutionized the analysis of complex compositions of organic compounds because of its high sensitivity and specificity. The great disadvantages of this technique were the high costs and the complexity of handling.

In the 1980s, both disadvantages were abolished by the development of inexpensive mass-selective detectors or ion trap detectors which can easily be handled. Both mass analysers allowed coupling with the modern high-performance capillary GC columns. As a consequence, GC–MS has become the most powerful method for the identification and determination of relatively apolar organic molecules, especially in complex matrices such as biosamples. However, many prerequisites have to be fulfilled. Suitable sample preparation is the most important prerequisite in the GC–MS of biosamples. It involves isolation and, if necessary, cleavage of conjugates and/or derivatization of the drugs and their metabolites.

1.1. Applicability of GC–MS in analytical toxicology

The choice of the method in analytical toxicology depends on the problems that have to be solved. Usually, the compounds that have to be analysed are unknown. Therefore, the first step is the identification of the compounds of interest. The analytical strategy first includes a screening test and second a confirmatory test. If only a single drug or a single category of drugs are to be monitored, immunoassays, if available, can be used for screening in order to differentiate between negative and presumptively positive samples. Positive results must be confirmed by a second independent method that is at least as sensitive as the screening test and that provides the highest level of confidence in the result. Without doubt, GC–MS is the reference method for confirmation of positive screening tests [1–5]. This two-step procedure is employed in areas of toxicology in which only those drugs or poisons have to be determined that are scheduled by law (*e.g.*, narcotics) or by international organizations such as the International Olympic Committee (doping agents).

Unfortunately, neither suicides nor murders are confined to scheduled drugs. Especially in clinical toxicology, the screening strategy must be more extensive, because more than 7000 drugs or pesticides are on the market worldwide [6]. For these reasons, a systematic procedure for toxicological analysis is necessary that allows the simultaneous detection of as many toxicants in biosamples as possible. In these instances, also the screening must be performed by GC–MS, *e.g.*, by using reconstructed mass chromatograms which may indicate the presence of suspected mass spectra in the stored full-scan run. Positive signals can then be confirmed by visual or computerized comparison of the peak underlying full mass spectra with reference spectra. In summary, GC–MS is the method of choice for screening and confirmation of toxicants that are volatile in GC.

1.2. Importance of the procedures reviewed for clinical toxicology, forensic toxicology and doping control

The predominant problem in clinical toxicology is the diagnosis, or the definite exclusion of an acute or a chronic intoxication. Furthermore, patients addicted to alcohol, medicaments or illegal drugs have to be monitored. For the determination of clinical death as a prerequisite for explantation of organs, the presence of drugs, which may depress the central nervous system, must be analytically excluded. The compliance of patients can be monitored by the determination of the prescribed drugs. Finally, monitoring of drugs with a narrow margin of therapeutic safety can be performed by the clinical toxicologist. Similar problems arise in forensic toxicology.

The predominant problems in forensic toxicology are the proof of an abuse of illegal drugs or of a murder by poisoning. Further, the forensic toxicologist has to detect drugs that may reduce the penal responsibility of a criminal, or which may reduce the fitness to drive a vehicle.

In doping control, the use or abuse of drugs which may stimulate the building up of muscles, the endurance during competition and which may reduce the pain caused by offences must be monitored.

The basis of a competent analytical and toxicological judgement and consultation is an efficient toxicological analysis. As the drugs are usually unknown, they have to be identified before determination in plasma is possible. Because of the serious clinical or legal consequences toxicological analyses have to be of high exactness. The reviewed GC–MS procedures satisfy most of these requirements.

1.3. Choice of the biosamples for systematic toxicological analyses of drugs

The concentrations of drugs are relatively high in urine, so that this is the sample of choice for screening and identification of unknown drugs or poisons. However, the metabolites of these drugs must be identified in addition or even exclusively. Nearly all of the reviewed papers describe methods for urine analysis.

Plasma is the sample of choice for quantification. However, the drug concentrations in plasma are too low for screening. Procedures for plasma analysis have only been described for some benzodiazepines [7], cocaine [8], metamphetamine [9], lysergide [10], tetrahydrocannabinol metabolites [11] and 6-monoacetylmorphine [12]. Toxicological analyses of hair samples allow the detection of past or chronic intoxications. Papers concerning hair analysis were reviewed by Moeller [13].

1.4. Sample preparation

Suitable sample preparation is an important prerequisite for the chromatography of biosamples. It involves the isolation and, if necessary, cleavage of conjugates and/or derivatization of the drugs and their metabolites. Isolation was performed by liquid–liquid extraction at a pH at which the analyte is non-ionized (see LLE in the Work-up column in Tables 1–16) or by solid-phase extraction (see SPE), preceded or followed by clean-up steps (see CU). Subsequently, the extract is concentrated. In the author's experience, solid-phase extraction is preferable if particular substances have to be selectively isolated in series from relatively homogeneous samples such as plasma samples in pharmacokinetic studies or urine samples for confirmation of a single drug [8,12,14–22]. Universal liquid–liquid extraction procedures are preferable for "general unknown analysis" procedures in emergency cases [6,23–40] because substances with very different physico-chemical properties must be isolated from heterogeneous matrices.

Conjugates can be cleaved by gentle but time-consuming enzymatic hydrolysis (see EN) in drug abuse or doping control studies. In toxicological analysis, especially in emergency cases, it is preferable to cleave the conjugates by rapid acid hydrolysis (see HY). However, the formation of artifacts during this procedure must be considered [6]. Derivatization steps are necessary if relatively polar compounds such as metabolites are to be

determined by GC–MS. In the reviewed papers, the following procedures were used: methylation (ME), propylation (PRO), trimethylsilylation (TMS), acetylation (AC), trifluoracetylation (TFA), pentafluoropropionylation (PFP), pentafluoropropylation (PFPRO), heptafluorobutylation (HFB), trifluoroacetylprolylation by (*S*)-(−)-trifluoroacetylprolyl chloride (TPC) and fluorobenzoylation by 4-fluorobenzoyl chloride (FBC); see Work-up column in Tables 1–16. Acetylation has been approved for the identification of numerous drugs and their metabolites [6,23–41]. It leads to stable derivatives with good GC properties. The acetylation mixture can be evaporated before analysis so that the resolution power of capillary columns does not decrease in contrast to other derivatization reagents (*e.g.*, TMS). The molecular mass does not increase very much, in contrast to TMS, TFA, PFP, etc., so that compounds with relatively high molecular mass and several derivatizable groups can be measured with inexpensive mass-selective detectors with a mass range only up to 650 u. Silylated or polyfluoroacylated derivates are unstable, especially in the presence of moisture [6,41], but nevertheless they are indispensable if relatively polar compounds with relatively high molecular masses (*e.g.*, LSD [10,42–44]) have to be determined by GC or GC–MS. Halogenated derivatives are necessary if compounds without electronegative sides (*e.g.*, LSD) are to be sensitively detected by negative-ion chemical ionization (NICI) MS [10,44] or by GC with electron-capture detection (ECD).

1.5. Choice of the references

The reviewed references were selected by online searching in the Medline database on CD-ROM (Silver Platter, Boston, London, Amsterdam, 1981–1991) and in the Chemical Abstracts Services (CAS) system. The period from January 1981 to September 1991 was taken into consideration. The search strategy was as follows: (barbiturate* or hypnotic* or anticonvuls* or benzodiazep* or antidepress* or neuroleptic* or stimulant* or hallucinogen* or analgesic* or antihistamin* or antiparkins* or beta or blocker* or beta blocker* or antiarrhythmic* or diuretic* or laxativ*) and (mass or spectr* or mass spectr* or screen*). Papers concerning the detection of illegal central stimulants and hallucinogens were considered only over the last five years, because many new developments were published in this period. The search strategy was as follows: (amfetam* or amphetam* or metamfetam* or methamphetam* or cocain* or LSD or lysergi* or phencyclid* or tetrahydrocannab* or THC or marihuan* or marijuan*) and (mass or spectr* or mass spectr* or MS) and (plasma or serum or blood or urine). The asterisk (*) is a "wild card" for any following character(s).

2. SYSTEMATIC TOXICOLOGICAL ANALYSIS OF PARTICULAR CLASSES OF DRUGS AND THEIR METABOLITES BY GC–MS

GC–MS procedures for the detection of drugs relevant to toxicology published in the last five to ten years are reviewed in this section according to the drug category. The principal information on each procedure is summarized in Tables 1–16 to simplify the rapid selection of a method suitable for an actual analytical problem.

The drugs are listed in the tables according to their international non-proprietary names (INN) or their common names. If only metabolites were determined "−M" is added to the name. If metabolites were determined additionally "+M" is given in the Drug column. The kind of biosample used is given in the Sample column (U = urine, P = plasma, B = blood, PS = pure substance). If urine samples of animals were studied the species is given in parentheses. The sample preparation discussed in any section is concisely summarized in the Work-up column. The principal information on the GC column, the mass spectral detection mode, the published reference data and the analytical detection limit are given. Reference data [*e.g.*, GC retention time or index (RT, RI), full mass spectra (MS) or selected fragment ions (FI)] are essential for the use of GC–MS in toxicology. For reasons of space, not all quality control data are listed. For toxicological screening procedures

TABLE I

GC–MS PROCEDURES FOR THE IDENTIFICATION OF BARBITURATES AND OTHER SEDATIVE–HYPNOTICS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Acecarbromal + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Allobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Amobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Amobarbital	U	LLE, ME	FSC HP-1 (110–250/25/50°C)	EI, SIM	MS, FI	20 ng/ml	46
Aprobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Barbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Brallobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Bromisoval	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Butabarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Butabarbital	U	LLE, ME	FSC HP-1 (110–250/25/50°C)	EI, SIM	MS, FI	20 ng/ml	46
Butalbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Butalbital	U	LLE, ME	FSC HP-1 (110–250/25/50°C)	EI, SIM	MS, FI	20 ng/ml	46
Butobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Carbromal + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Clomethiazole + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Crotylbarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Cyclobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Cyclopentobarbital	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Diethylallylacetamide[a]	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23

Dipropylbarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Glutethimide + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Guaifenesin + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Ethinamate[a]	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Heptabarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Hexobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Meprobamate	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Methaqualone + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Metharbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Methohexital	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Methylphenobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Methyprylone + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Pentobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Pentobarbital	U	LLE, ME	FSC HP-1 (110–250/25/50°C)	EI, SIM	MS, FI	20 ng/ml	46
Phenobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS,	th. conc.	23
Phenobarbital	U	LLE, ME	FSC HP-1 (110–250/25/50°C)	EI, SIM	MS, FI	20 ng/ml	46
Propallylonal + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS,	th. conc.	23
Pyrithyldione[a]	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS,	th. conc.	23
Sccobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS,	th. conc.	23
Secobarbital	U	LLE, ME	FSC HP-1 (110–250/25/50°C)	EI, SIM	MS, FI	20 ng/ml	46
Thiobutabarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS,	th. conc.	23
Thiopental + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS,	th. conc.	23
Tolylbarbiturate (IS)	U	LLE, ME	FSC HP-1 (110–250/25/50°C)	EI, SIM	MS, FI	20 ng/ml	46
Vinbarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS,	th. conc.	23
Vinylbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS,	th. conc.	23

[a] These compounds are destroyed during acid hydrolysis. They can only be detected in a direct extract of urine [6]. IS = internal standard.

TABLE 2

GC–MS PROCEDURES FOR THE IDENTIFICATION OF ANTICONVULSANTS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Carbamazepine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Clonazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	tox. conc.	24
Diazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Ethosuximide[a] + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Ethosuximide	PS, (U,P)[b]	LLE[b]	5% Poly-I-110 (80–260/10°C)	EI/CI/NICI, scan	MS	[b]	52
Ethotoin	PS, (U,P)[b]	LLE[b]	5% Poly-I-110 (80–260/10°C)	EI/CI/NICI, scan	MS	[b]	52
Mephenytoin + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Mesuximide + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Mesuximide	PS, (U,P)[b]	LLE[b]	5% Poly-I-110 (80–260/10°C)	EI/CI/NICI, scan	MS	[b]	52
Methylphenobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Paramethadione	PS, (U,P)[b]	LLE[b]	5% Poly-I-110 (80–260/10°C)	EI/CI/NICI, scan	MS	[b]	52
Phenobarbital + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Phensuximide	PS, (U,P)[b]	LLE[b]	5% Poly-I-110 (80–260/10°C)	EI/CI/NICI, scan	MS	[b]	52
Phenytoin + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Phenytoin	PS, (U,P)[b]	LLE[b]	5% Poly-I-110 (80–260/10°C)	EI/CI/NICI, scan	MS	[b]	52
Primidone + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Propylhexedrine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Sultiame	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Trimethadione[a]	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Trimethadione	PS, (U,P)[b]	LLE[b]	5% Poly-I-110 (80–260/10°C)	EI/CI/NICI, scan	MS	[b]	52

[a] These compounds are destroyed during acid hydrolysis. They can only be detected in a direct extract of urine [6].

[b] The paper cited presents EI, CI and NICI mass spectra. A procedure is described for extraction and GC separation of spiked urine and plasma samples but without any association with the mass spectra.

in urine, quality criteria of the parent compound are of minor value if the concentrations of the metabolites are much higher in urine than those of the parent drug and if the metabolites are detected by the procedure. Most of the toxicologically relevant drugs are lipophilic substances that undergo extensive metabolism. As pure substances of the metabolites are usually not available, it is necessary to control the quality of the screening procedures using urine samples from volunteers or in-patients treated with a known dose of the drug [23–40,45]. The procedure should be sufficiently sensitive to detect therapeutic concentrations at least over a 12–24 h period after ingestion (see th. conc. in the Detection limit column in Tables 1–16). In the author's experience, procedures are suitable for toxicological purposes if this prerequisite is met.

2.1. Barbiturates, other sedative–hypnotics and their metabolites

Barbiturates are still used and misused, but with a decreasing tendency. They may reduce the fitness to drive a vehicle or to work at machines and they may lead to addiction or to severe intoxication. Therefore, screening for barbiturates is necessary in clinical, forensic and occupational toxicology. As barbiturates are scheduled drugs, immunoassays are available which can be used for screening.

Some papers describe the GC–MS confirmation of positive immunoassay results [46–48] (Table 1). In the author's experience, methylation [46] is not necessary in clinical toxicology, because the barbiturate concentrations in urine are relatively high. Unfortunately, two papers [47,48] gave no information on how the barbiturates should be detected by MS [selected-ion monitoring (SIM) or scan mode, which ions, which spectra, etc.?]. A procedure was described for the detection of barbiturates and their metabolites [23] integrated in a systematic toxicological analysis (see Section 3). As this analysis includes also several categories of basic drugs with conjugated metabolites [28–32,34,35,37–40], acid hydrolysis followed by extraction at pH 8–9 was used for barbiturates also. This general screening and confirmation procedure allowed the detection of therapeutic concentrations of barbiturates. Papers concerning the determination of barbiturates and other sedative–hypnotics were reviewed by Gupta [49].

2.2. Anticonvulsants

Anticonvulsants are usually not abused but they relatively often lead to accidental, iatrogenic or suicidal intoxications. They may reduce the fitness to drive a vehicle or to work at machines. For these reasons a screening procedure for anticonvulsants is necessary. Immunoassays are available for drug monitoring of particular drugs in plasma. As the class of anticonvulsants is chemically heterogeneous, there is no immunoassay for screening of the whole class of drugs.

Many papers have been published on the determination of antiepileptics [50,51], but only one on identification by GC–MS [24] (Table 2). Again, this procedure is integrated in a general screening and confirmation procedure (see Section 3) that allowed the detection of therapeutic concentrations of anticonvulsants with the exception of the low-dosed clonazepam. Ishikawa *et al.* [52] presented electron-impact ionization (EI), chemical ionization (CI) and NICI mass spectra of some antiepileptics recorded using the direct inlet system. They did not consider that several drugs are decomposed during sample preparation and/or GC [6]. The described extraction and GC procedure was not used for recording of the mass spectra. Only solutions of the pure substances were injected into the GC–MS system to compare the sensitivities of the three ionization techniques. As the common EI mode was the most sensitive, publishing of the CI and NICI mass spectra is useless for toxicological purposes. The same group have published in further papers of the same type EI, CI and NICI mass spectra of benzodiazepines [53,54] and antidepressants [55].

2.3. Benzodiazepines

Benzodiazepines are used as tranquillizers,

TABLE 3

GC–MS PROCEDURES FOR THE IDENTIFICATION OF BENZODIAZEPINES AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Alprazolam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	tox. conc.	32,67
Alprazolam + M	U	EN, LLE, TMS	FSC DB-1 (250–300/15°C)	EI, SIM	RT, FI	300 ng/ml	56
Alprazolam M	U	EN, LLE, TMS	FSC HP-1 or-5 (140–320/30/50°C	EI, SIM	RT, FI	50 ng/ml	57
Alprazolam	U	HY, LLE	FSC HP-1 (140–285/20°C)	EI, scan	MS	?	59
Bromazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Bromazepam (IS)	U	EN, LLE, TMS	FSC HP-1 or-5 (140–320/30/50°C)	EI, SIM	RT, FI	50 ng/ml	57
Bromazepam	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Brotizolam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	tox. conc.	32,67
Camazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Chlordiazepoxide	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Chlordiazepoxide	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Clobazam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Clobazam + M	P	LLE, TMS	FSC HP-1 (70–300/20°C)	EI, scan or SIM	MS	1–5 ng/ml	7
Clonazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	tox. conc.	32
Clonazepam + M	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Clorazepate + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Clorazepate	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Clotiazepam[a]	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Cloxazolam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Delorazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Diazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Diazepam-M	U	EN, LLE, TMS	FSC HP-1 or-5 (140–320/30/50°C)	EI, SIM	RT, FI	50 ng/ml	57
Diazepam + M	P	LLE, TMS	FSC HP-1 (70–300/20°C)	EI, scan or SIM	MS	1–5 ng/ml	7
Diazepam + M	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Ethyl loflazepate	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Flunitrazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	tox. conc.	32
Flunitrazepam + M	P	LLE, TMS	FSC HP-1 (70–300/20°C)	EI, scan or SIM	MS	1–5 ng/ml	7
Flunitrazepam + M	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Flurazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Halazepam + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		32
Haloxazolam	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Ketazolam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Loprazolam	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		32

Lorazepam	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Lorazepam	U	EN, LLE, TMS	FSC HP-1 or-5 (140–320/30/50°C)	EI, SIM	RT, FI	50 ng/ml	57
Lorazepam	P	LLE, TMS	FSC HP-1 (70–300/20°C)	EI, scan or SIM	MS	5 ng/ml	7
Lorazepam	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Lormetazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Medazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Medazepam + M	PS, (UP)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Metaclazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Midazolam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Midazolam + M	U	EN, LLE, TMS	FSC DB-1 (240 300/15°C)	EI, SIM	RT, FI	< 300 ng/ml	58
Midazolam + M	U	EN, LLE, TMS	FSC HP-1 or-5 (140–320/30/50°C)	EI, SIM	RT, FI	50 ng/ml	57
Midazolam	U	HY, LLE	FSC HP-1 (140–285/20°C)	EI, scan	MS	?	59
Midazolam + M	P	LLE, TMS	FSC HP-1 (70–300/20°C)	EI, scan or SIM	MS	?	7
Nitrazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Nitrazepam	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Nordazapam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Nordazepam	U	EN, LLE, TMS	FSC HP-1 or-5 (140 320/30/50°C)	EI, SIM	RT, FI	50 ng/ml	57
Nordazepam	P	LLE, TMS	FSC HP-1 (70–300/20°C)	EI, scan or SIM	MS	1–5 ng/ml	7
Oxazepam	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Oxazepam	U	EN, LLE, TMS	FSC HP-1 or-5 (140–320/30/50°C)	EI, SIM	RT, FI	50 ng/ml	57
Oxazepam	P	LLE, TMS	FSC HP-1 (70–300/20°C)	EI, scan or SIM	MS	5 ng/ml	7
Oxazepam	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Oxazolam + M	U	HY, LLE, AC	FSC HP-1 (100 310/30°C)	EI, scan	RI, MS	th. conc.	32
Oxazolam	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Prazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Prazepam + M	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Quazepam + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		32
Temazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Temazepam + M	P	LLE, TMS	FSC HP-1 (70 300/20°C)	EI, scan or SIM	MS	5 ng/ml	7
Temazepam + M	PS, (U,P)[b]	HY, SPE[b]	5% SP-2100 (220°C)	EI/CI/NICI, scan	RT, FI	[b]	53
Tetrazepam + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Triazolam + M	U	HY, LLE, AC	FSC HP-1 (100 310/30°C)	EI, scan	RI, MS	tox. conc.	32,67
Triazolam + M	U	EN, LLE, TMS	FSC HP-1 or-5 (140–320/30/50°C)	EI, SIM	RT, FI	50 ng/ml	57
Triazolam	U	HY, LLE	FSC HP-1 (140–285/20°C)	EI, scan	MS	?	59
Triazolam + M	P	LLE, TMS	FSC HP-1 (70–300/20°C)	EI, SIM	MS	?	7

[a] This compound is destroyed during acid hydrolysis. As its metabolites are conjugated, they can only be detected after enzymatic hydrolysis [6].

[b] The paper cited presents EI, CI and NICI mass spectra recorded using the direct inlet system. A procedure is described for extraction and GC separation of spiked urine and plasma samples but this was not used for recording of the mass spectra.

hypnotics, anticonvulsants or muscle relaxants and belong to the most frequently prescribed drugs. They may reduce the fitness to drive a vehicle or to work at machines and they may lead to addiction or severe intoxication, especially in combination with alcohol. Therefore, screening for benzodiazepines is necessary in clinical, forensic and occupational toxicology. Immunoassays are available for screening.

As some of the benzodiazepines and their metabolites are excreted in urine in a completely conjugated form, cleavage of conjugates is the first step of the sample preparation. Both enzymatic hydrolysis [56–58] and acid hydrolysis [32,53,59] have been used (Table 3). During acid hydrolysis 1,4- and 1,5-benzodiazepines are cleaved to benzophenone derivatives or analogues. Detection of these hydrolysis products by GC–MS was first described by Maurer and Pfleger [60]. However, the sensitivity could be improved considerably by acetylation of the primary amino and phenolic hydroxy groups of the benzophenones [32]. This procedure was the basis of a systematic toxicological analysis for several categories of drugs (see Section 3). Jones *et al.* [59] completed this procedure, recommending further fragment ions for screening of alprazolam, midazolam and triazolam. Unfortunately, they did not conclude whether these low-dosed benzodiazepines could really be detected or not. In the author's experience, midazolam could be detected after a therapeutic dose [32], whereas alprazolam and triazolam were found only after intoxications. Further papers described the screening and confirmation for alprazolam, midazolam and triazolam after low dosage [56–58]. Drouet-Coassolo *et al.* [7] described the identification and determination of unconjugated benzodiazepines and their metabolites in plasma using GC–MS after trimethylsilylation. The procedure was exemplified only for relatively highly dosed benzodiazepines (clobazam, temazepam and lorazepam). Several other papers deal exclusively with the documentation of reference mass spectra without any association with bioanalytical procedures [54,61–63]. Further chromatographic procedures were reviewed by Sioufi and Dubois [64].

2.4. Antidepressants

Antidepressants are often the cause of intoxication because many depressive patients are likely to commit suicide. Therefore, a systematic toxicological screening (see Section 3) must cover these drugs. Maurer and Pfleger [35] described in 1984 a GC–MS screening using packed columns (Table 4). In the meantime, testing confirmed that modern capillary columns lead to the same or better results [65–67]. The published GC retention indices correspond with those measured on capillary columns [67,68]. Suzuki *et al.* [55] presented EI, CI and NICI mass spectra of some antidepressants recorded using the direct inlet system. They did not consider that several drugs (*e.g.*, N-oxides) are decomposed during sample preparation and/or GC [6]. The described extraction and GC procedure was not used for recording of the mass spectra. Procedures for the determination of antidepressants were reviewed by Norman and Maguire [69].

2.5. Phenothiazine and butyrophenone neuroleptics

Neuroleptics have supressant effects on the consciousness and respiration. They have an anticholinergic effect in the autonomic nervous system. As overdosages lead to severe intoxications, rapid diagnosis is required. Immunoassays are not available, so that screening must be performed directly by GC–MS. Maurer and Pfleger described in 1984 a GC–MS screening for phenothiazine [38] and butyrophenone [39] neuroleptics (Table 5 and 6). As discussed in Section 2.4, the packed column can be replaced with a capillary column.

2.6. Central stimulants

Central stimulants are drugs of abuse in addition to doping agents. Immunoassays are available for amphetamine and methamphetamine, for derivatives of amphetamine including other sympathomimetics (*e.g.*, Abbot TDx amphetamine class) and for cocaine. Several papers described GC–MS confirmation of amphetamines

TABLE 4

GC–MS PROCEDURES FOR THE IDENTIFICATION OF ANTIDEPRESSANTS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Amitriptyline + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Amitriptyline	PS, (U,P)[c]	SPE[c]	5% SP-2100 (220 or 280°C)	EI/CI/NICI, scan	RT, MS	–[c]	55
Amitriptyline oxide + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Clomipramine + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Clomipramine	PS, (U,P)[c]	SPE[c]	5% SP-2100 (220 or 280°C)	EI/CI/NICI, scan	RT, MS	–[c]	55
Desipramine + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Desipramine	PS, (U,P)[c]	SPE[c]	5% SP-2100 (220 or 280°C)	EI/CI/NICI, scan	RT, MS	–[c]	55
Dibenzepin + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Dimetacrine[a]	U (rat)	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS		35
Doxepin + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Imipramine + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Imipramine + M	PS, (U,P)[c]	SPE[c]	5% SP-2100 (220 or 280°C)	EI/CI/NICI, scan	RT, MS	[c]	55
Lofepramine + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Lofepramine	PS, (U,P)[c]	SPE[c]	5% SP-2100 (220 or 280°C)	EI/CI/NICI, scan	RT, MS	–[c]	55
Maprotiline + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Melitracene + M	U (rat)	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS		35
Mianserin + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Nomifensine + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Nortriptyline + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Noxiptyline + M	U (rat)	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS		35
Opipramol + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Protriptyline + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35,67
Tranylcypromine	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Trazodone + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35,67
Trimipramine + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35,65
Trimipramine	PS, (U,P)[c]	SPE[c]	5% SP-2100 (220 or 280°C)	EI/CI/NICI, scan	RT, MS	[c]	55
Viloxazine + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35

[a] This compound is destroyed during acid hydrolysis. It can only be detected in a direct extract of urine [6].

[b] Testing confirmed that the packed column described in the paper cited can be replaced by the given FSC HP-1 [66,67]. The given retention indices correspond to those measured on the FSC [67,68].

[c] The paper cited presents EI, CI and NICI mass spectra recorded using the direct inlet system. A procedure is described for extraction and GC separation of spiked urine and plasma samples but this was not used for recording of the mass spectra.

TABLE 5

GC–MS PROCEDURES FOR THE IDENTIFICATION OF PHENOTHIAZINE NEUROLEPTICS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Acepromazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38,67
Acepromethazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Alimemazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Butaperazine + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Chlorpromazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Chlorprothixene + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Clopenthixol + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38,67
Clozapine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Dixyrazine + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Flupenthixol + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Fluphenazine + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Homophenazine + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Levomepromazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Oxypertine + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Pecazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38,67
Perazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Periciazine + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Perphenazine + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Prochlorperazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38,67
Promazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Promethazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Prothipendyl + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Sulphoridazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Tetrabenazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Thiopropazate	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Thioproperazine + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		38
Thioridazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Trifluoperazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38,67
Triflupromazine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38

[a] Testing confirmed that the packed column described in the paper cited can be replaced by the given FSC HP-1 [66,67]. The given retention indices correspond to those measured on the FSC [67,68].

TABLE 6

GC–MS PROCEDURES FOR THE IDENTIFICATION OF BUTYROPHENONE NEUROLEPTICS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Benperidol–M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	39
Bromperidol + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	39
Droperidol–M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	tox. conc.	39
Fluanisone + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		39
Fluspirilene–M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	tox. conc.	39
Haloperidol + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	39
Melperone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	39
Moperone + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		39
Penfluridol–M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	39
Pimozide–M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	tox. conc.	39
Pipamperone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	39
Trifluperidol–M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	39

[a] Testing confirmed that the packed column described in the paper cited can be replaced by the given FSC HP-1 [66,67]. The given retention indices correspond to those measured on the FSC [67,68].

TABLE 7

GC–MS PROCEDURES FOR THE IDENTIFICATION OF CENTRAL STIMULANTS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
(*R,S*)-Amphetamine	U	SPE, HFB	FSC CB-5 (110–220/10/30°C)	EI, SIM	RT, FI	35 ng/ml	14
(*R,S*)-Amphetamine + M	U (monkey)	EN, LLE, HFB	2% OV-17 (150°C)	EI, SIM	RT, FI	25 ng/ml	70
(*R,S*)-Amphetamine	U	LLE, TFA	FSC HP-1 (100–190/20°C)	EI, SIM	RT, FI	25 ng/ml	71
(*R,S*)-Amphetamine	U	LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	10 ng/ml	76
(*R*)-(−)-Amphetamine[a]	U	LLE, TPC	FSC HP-1 (190°C)	EI, scan	RI, MS	100 ng/ml	75,76
(*R,S*)-Bamethan	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Cocaine + M	U	LLE, PFP, PFPRO	FSC HP-1 (165–225/30°C)	EI, SIM	RT, FI	25 ng/ml	71
Cocaine + M	U	LLE, PFP, PFPRO	FSC HP-1 (165–225/30°C)	EI, SIM	MS, FI	12.5 ng/ml	73
Cocaine + M	B, U	SPE, PRO, FBC	FSC HP-1 (100–260/30°C)	EI, SIM	MS, FI	?	8
Cocaine + M	U	SPE, TMS	FSC HP-Ultra 1 (150–275/20°C)	EI, SIM	FI	50 ng/ml	15
(*R,S*)-Etilefrine	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
(*R,S*)-Hydroxyamphetamine	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
(*R,S*)-Hydroxynorephedrine	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
(*R,S*)-Metamphetamine	B	LLE, CU, TFA	5% OV-17 (180°C)	EI/CI, SIM	MS, RT, FI	?	9
(*R,S*)-Metamphetamine	U	SPE, HFB	FSC CB-5 (110–220/10/30°C)	EI, SIM	RT, FI	35 ng/ml	14
(*R,S*)-Metamphetamine + M	U (monkey)	EN, LLE, HFB	2% OV-17 (150°C)	EI, SIM	RT, FI	25 ng/ml	70
(*R,S*)-Metamphetamine	U	LLE, TFA	FSC HP-1 (100–190/20°C)	EI, SIM	RT, FI	25 ng/ml	71
(*R,S*)-Metamphetamine	U	LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	10 ng/ml	76
(*R*)-(−)-Metamphetamine[a]	U	LLE, TPC	FSC HP-1 (190°C)	EI, scan	RI, MS	100 ng/ml	75,76
(*R*)-(−)-Metamphetamine[a]	U	LLE, TPC	FSC HP-1 (130–250/20°C)	EI, SIM	RT, FI	<375 ng/ml	74
(*R*)-(−)-Metaraminol	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
(*R,S*)-Norfenefrine	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
(*R,S*)-Octopamine (Oxedrine, see Synephrine)	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Phentermine (IS)	U (monkey)	EN, LLE, HFB	2% OV-17 (150°C)	EI, SIM	RT, FI	25 ng/ml	70
(*R*)-(−)-Phenylefrine	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
(*R,S*)-Pholedrine	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Selegiline + M	U	LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	10 ng/ml	76
Selegiline + M[a]	U	LLE, TPC	FSC HP-1 (190°C)	EI, scan	RI, MS	100 ng/ml	75,76
(*R,S*)-Synephrine	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Tyramine	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72

[a] This enantioselective GC–MS procedure allows the differentiation between (*R*)-(−)- and (*S*)-(+)-enantiomers of amphetamine and metamphetamine.

[9,14,70,71], of phenolalkylamines [72] and of cocaine [8,15,71,73] (Table 7). Solid-phase or liquid–liquid extraction at alkaline pH was described for amphetamine and its derivatives followed by acylation of the amino group (Table 7). Phenolalkylamines require cleavage of conjugates prior to extraction, because the phenolic hydroxy group is conjugated [70,72].

Cocaine was isolated by solid-phase or liquid–liquid extraction at pH 7–9 (Table 7), followed by pentafluoropropylation of benzoylecgonine and pentafluoropropionylation of methylecgonine [71,73] or by propylation and fluorobenzoylation [8] or trimethylsilylation [15]. The sensitivity of all procedures was sufficient to confirm positive immunoassay results.

The problems arising from silylation and perfluoroacetylation were already discussed in Section 1.4. A further problem arises from the enantioselective differences in the pharmacological activity of the amphetamines. Only the (*S*)-(+)-enantiomers are addictive and therefore scheduled by law. The immunoassays and the confirmation tests are achiral procedures, so that they cannot differentiate between the enantiomers. However, there are medicaments on the market which contain only the (*R*)-(−)-enantiomer of methamphetamine (*e.g.*, Vicks Nasal Inhalator [74]) or which are metabolized to the (*R*)-(−)-enantiomers of metamphetamine and amphetamine (*e.g.*, selegiline [75,76]). For differentiation of the intake of these medicaments from an abuse of (met)amphetamine, enantioselective GC–MS procedures have been published [74–76].

Two further papers [77,78] indicate that MS procedures were used. Unfortunately, in both papers only the apparatus and the sample preparation were given, and no information on how the drugs should be analysed by MS.

2.7. Hallucinogens

Cannabis (marijuana) is the most frequently abused illegal drug. Lysergide (LSD) and phencyclidine are more rarely abused, but the margin of therapeutic safety is smaller. Immunoassays are available for the three hallucinogens and confirmation by GC–MS was described in the last few years (Table 8).

The detection of LSD is complicated because the concentrations are very low and the molecule is not very volatile. However, after suitable sample preparation including derivatization, LSD could be detected [10,42–44]. Using the procedure of Francom *et al.* [43], some intoxications with LSD could be identified. Paul *et al.* [42] compared the efficiencies of clean-up steps by acid–base purification and by solid-phase extraction. In Fig. 1, ion chromatograms are shown of (a) an extracted standard solution (400 pg/ml LSD), (b) an extracted urine sample (501 pg/ml LSD) after acid–base purification and (c) after solid-phase purification [42]. As shown, solid-phase purification was more effective than acid–base purification. This example shows that effective clean-up steps may be necessary for very sensitive detection.

Phencyclidine and one metabolite could be detected after solid-phase or liquid–liquid extraction using the SIM mode [16,71].

Several papers have been published on the detection of the main urinary metabolite of tetrahydrocannabinol (THC), the scheduled and pharmacologically active ingredient of hashish and marijuana. As the main metabolite of THC, 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), is excreted as the ester glucuronide, the conjugate must be cleaved by alkaline hydrolysis (alk. HY in Work-up column in Table 8). After solid-phase or liquid–liquid extraction at a weakly acidic pH, THC-COOH was derivatized by methylation [17–19,71], pentafluoropropylation and pentafluoropropionylation [79] and trimethylsilylation [11,71,80]. Clean-up steps were employed before or after extraction to improve the sensitivity. In the author's experience, methylation and the full-scan mode are sufficient to detect at least 20 ng/ml THC-COOH [6]. Detection of lower concentrations leads to problems in the toxicological interpretation of the result, because passive smoking must be considered.

TABLE 8

GC–MS PROCEDURES FOR THE IDENTIFICATION OF HALLUCINOGENS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Lysergide (LSD)	U	CU, LLE/SPE, TMS	FSC DB-5 (190–290/20°C)	EI, SIM	RT, FI, MS	0.3 ng/ml	42
Lysergide (LSD)	U	LLE, TMS	FSC HP-1 (220–310/20°C)	EI, SIM	RT, FI, MS	0.5 ng/ml	43
Lysergide (LSD)	U	EN, CU, LLE, TFA	FSC HP-1 (160–300/20°C)	NICI, SIM	RT, FI, MS	0.25 ng/ml	44
Lysergide (LSD)	P	LLE, TFA	FSC HP-Ultra 1 (180–300/20°C)	NICI, SIM	FI	0.1 ng/ml	10
Phencyclidine	U	LLE	FSC HP-1 (100–190/20°C)	EI, SIM	RT, FI	10 ng/ml	71
Phencyclidine – M	U	SPE	FSC DB-1 (200°C)	EI, SIM	FI	2 ng/ml	16
THC-COOH	B	EN, LLE, TMS	FSC BP-1 (160–280/39°C)	EI, SIM	MS, FI	?	11
THC-COOH	U	alk, HY, SPE, ME	?	EI, scan	MS	5 ng/ml	17
THC-COOH	U	alk, HY, SPE, ME	FSC SPB-1 (200–270/5°C)	EI, scan	MS	20 ng/ml	18
THC-COOH	U	alk, HY, SPE, ME	FSC DB-5 (245°C)	EI, SIM	FI, MS	2 ng/ml	19
THC-COOH	U	alk, HY, LLE, ME	FSC HP-1 (165–250/50°C)	EI, SIM	RT, FI	15 ng/ml	71
THC-COOH	U	alk, HY, SPE, PRO	FSC DB-1 (200–280/50/12°C)	EI, SIM	MS	10 ng/ml	20
THC-COOH	U	alk, HY, LLE, PFP, PFPRO	FSC DB-5 (180–270/15°C)	EI, SIM	FI	1.8 ng/ml	79
THC-COOH	U	alk, HY, LLE, TMS	FSC BP-1 (160–280/39°C)	EI, SIM	MS, FI	?	11
THC-COOH	U	alk, HY, CU, LLE, TMS	FSC HP-1 (100–280/1/10/25°C)	EI, SIM	RT, FI	5 ng/ml	80
THC-COOH	U	alk, HY, LLE, TMS	FSC HP-1 (165–250/50°C)	EI, SIM	RT, FI	10 ng/ml	71

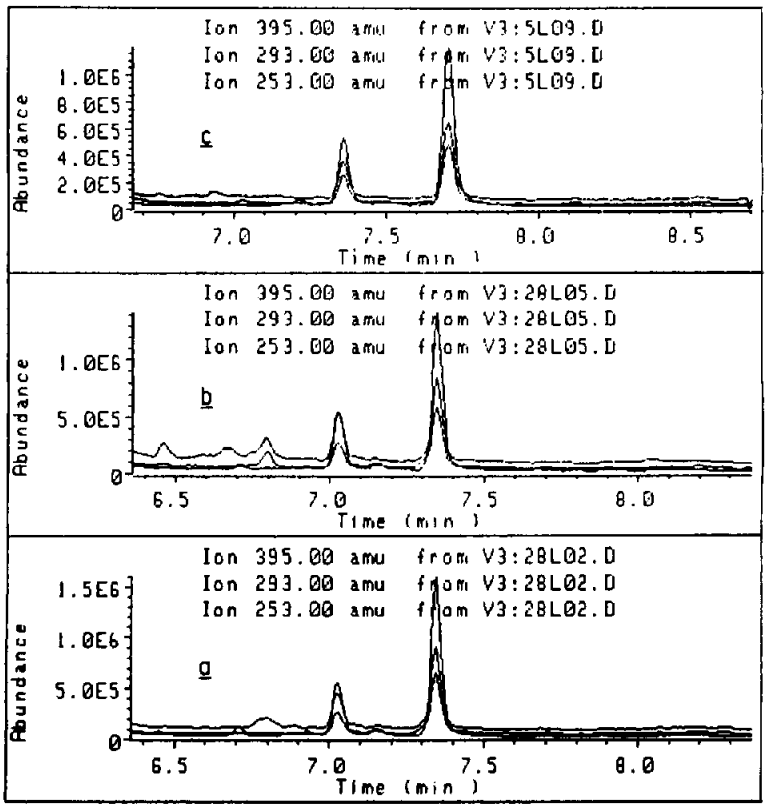

Fig. 1. Chromatograms (SIM) of (a) an extracted standard (400 pg/ml LSD), (b) an extracted urine sample (501 pg/ml LSD) after acid–base purification and (c) after solid-phase purification [42]. Details of the method are summarized in Table 8.

2.8. Opioid (narcotic) and other potent analgesics

Opioid analgesics, often named narcotics, are widely used to reduce severe pain especially in a postoperative state and in the final state of cancer diseases. Further, they are abused because of their euphoriant and anxiolytic effects. While opioid medicaments are usually misused by medical staff, heroin is widely abused by drug addicts. If heroin is not available the addicts often take opioid medicaments. For legal reasons, the application of heroin must analytically be differentiated from an intake of other opioids. Therefore, 6-monoacetylmorphine (6-MAM), the only heroin specific metabolite, must be detected in plasma [12] or urine. Several papers have appeared concerning the detection of 6-MAM (Table 9). After solid-phase or liquid–liquid extraction at a weakly alkaline pH 6-MAM was derivatized by trifluoroacetylation [81], pentafluoropropionylation [12,22], propionylation [21] or trimethylsilylation [82]. The TMS procedure showed the lowest sensitivity.

Screening procedures were described for the detection of most of the opioids and other potent analgesics after acid hydrolysis, liquid–liquid extraction at pH 8–9 followed by acetylation [37,41,83] or trimethylsilylation [72] (Table 9). These procedures did not allow the differentiation of heroin from other opioids because MAM is cleaved to morphine during hydrolysis and artificially reacetylated.

The antitussive pholcodine was found to interfere with opiate immunoassays, although it does not bind to opiate receptors [83]. Pholcodine is partly hydrolysed to morphine by hydrochloric

TABLE 9

GC–MS PROCEDURES FOR THE IDENTIFICATION OF OPIOIDS (NARCOTICS) AND OTHER POTENT ANALGESICS AND THEIR METABOLITES IN *BIOSAMPLES*

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Cetobemidone + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		37
Codeine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Codeine + M	U	HY, LLE, AC	FSC DB-5 (240°C)	EI, SIM	RT, FI, MS	?	41
Codeine + M	U	HY, LLE, PFP	FSC HP-1 (165–240/30°C)	EI, SIM	RT, FI	50 ng/ml	71
Codeine + M	U	HY, LLE, TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Dextromoramide	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		37
Dihydrocodeine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Dihydrocodeine	U	HY, LLE, TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Dihydromorphine	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Ethylmorphine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37,67
Ethylmorphine	U	HY, LLE, TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Heroin + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Heroin–M (6-MAM)	U	LLE, TFA	FSC BP-10 (240°C)	EI, scan	MS	2 ng/ml	81
Heroin–M (6-MAM)	U	LLE, TMS	FSC HP-1 (?°C)	EI, SIM	RT, FI	10 ng/ml	82
Heroin–M (6-MAM)	U	SPE, PRO	FSC DB-5 (130–250°C)	EI, scan	MS	0.8 ng/ml	21
Heroin–M (6-MAM)	U	SPE, PFP	FSC HP-5 (230°C)	EI, SIM	RT, FI, MS	2 ng/ml	22
Heroin–M (6-MAM)	B	SPE, PFP	FSC DB-5 (150–256/50/5°C)	EI, SIM	RT, FI	0.5 ng/ml	12
Hydrocodone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Hydromorphone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37,67
Levorphanol + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37,67

Levorphanol (Meperidine, see Pethidine)	U	HY, LLE. TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Methadone + M	U	HY, LLE, (AC)	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Methadone	U	HY, LLE, (TMS)	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Methorphan + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Morphine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Morphine	U	HY, LLE, AC	FSC DB-5 (240°C)	EI, SIM	RT, FI, MS	?	41
Morphine	U	HY, LLE, PFP	FSC HP-1 (165–240/30°C)	EI, SIM	RT, FI	50 ng/ml	71
Morphine	U	HY, LLE, TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Nalorphine (IS)	U	HY, LLE, AC	FSC DB-5 (240°C)	EI, SIM	RT, FI MS	?	41
Naloxone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Nefopam + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Normethadone + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		37
Oxycodone + M	U (rat)	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS		37
Pentazocine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Pentazocine	U	HY, LLE, TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Pethidine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Phenazocine	U	HY, LLE, TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Pholcodine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	3 ng/ml	83
Propoxyphen − M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Thebacone − M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37,67
Tilidine − M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Tramadol + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37

[a] Testing confirmed that the packed column described in the paper cited can be replaced by the given FSC HP-1 [66,67]. The given retention indices correspond to those measured on the FSC [67,68].

acid, so that careful enzymatic hydrolysis must be used if both pholcodine and morphine were found in urine.

One paper was found by the Medline search with a title indicating a GC–MS procedure [78]. However, no GC–MS data could be found in it.

2.9. Non-opioid analgesics

Non-opioid analgesics are widely used as over-the-counter drugs. Patients with chronic pain states misuse these drugs without control by physicians. A GC–MS procedure for screening and confirmation of non-opioid analgesics was described for the detection of an acute intoxication (*e.g.*, with paracetamol) or of an abuse [40] (Table 10). As discussed in Section 2.4, the packed column can be replaced by a capillary column.

2.10. Antihistamines (histamine H_1-receptor blockers)

Blockers of the histamine H_1-receptor (antihistamines) are used as allergy remedies, non-prescription hypnotics and in combination with other drugs as cold medicines. Antihistamines, often combined with other drugs or alcohol, reduce the fitness to drive a vehicle or work with machines and they often are the cause of intoxication. Therefore, screening for antihistamines is necessary in clinical, forensic, and occupational toxicology.

The identification of fifty H_1-blockers and their metabolites in urine has been described [28–31] (Table 11). These procedures allowed the rapid and specific detection and differentiation of therapeutic concentrations of alkanolamine, alkylamine, ethylenediamine, piperazine and phenothiazine antihistamines (H_1-blockers). They were integrated in a systematic screening procedure that will be discussed in Section 3. Further chromatographic procedures were reviewed by Maurer [84].

2.11. Antiparkinsonian drugs

Antiparkinsonian drugs may lead to severe intoxication because of their central depressive and anticholinergic properties. Toxicological detection of these drugs was described as part of a systematic screening and confirmation procedure [34] (Table 12). As discussed in Section 2.4, the packed column can be replaced by a capillary column. Selegiline, a new antiparkinsonian, is of special interest since it is metabolized to (*R*)-(−)-metamphetamine and (*R*)-(−)-amphetamine, which interfere with immunoassays for amphetamines [75,76]. Enantioselective procedures are discussed in Section 2.6. Papers concerning the determination of antiparkinsonians were reviewed by Schwarz *et al.* [85].

2.12. β-Blockers (β-adrenoceptor blockers)

β-Adrenoceptor blockers (β-blockers), are widely used and therefore frequently encountered in clinical and forensic analysis. From 1988 the medical commission of the IOC has forbidden the abuse of β-blockers in sports. GC–MS procedures have been published for both indications (Table 13). Maurer and Pfleger described in 1986 [33] the identification of 23 β-blockers and their metabolites in urine by GC–MS after acid hydrolysis and acetylation integrated in a systematic screening procedure (see Section 3). During hydrolysis atenolol, carazolol, mepindolol and pindolol are destroyed [33]. Lho *et al.* [72] described the detection of *e.g.*, atenolol after acid hydrolysis, but apparently did not make studies using spiked or authentic urine samples after the complete sample preparation. In the author's experience, this is essential for the development of toxicological analysis procedures. Delbeke *et al.* [86,87] and Leloux and co-workers [45,88] employed enzymatic hydrolysis followed by solid-phase extraction and trifluoroacetylation combined with silylation for doping analysis. In contrast to emergency analysis, time-consuming enzymatic hydrolysis is preferable for doping control. Delbeke *et al.* [87] compared the effectiveness of conventional liquid–liquid extraction and solid-phase extraction using Extrelut-1, Extrelut-3 and C_{18}. The best detection limits of the GC-MS procedure were achieved after liquid–

TABLE 10

GC–MS PROCEDURES FOR THE IDENTIFICATION OF NON-OPIOID ANALGESICS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
(Acetaminophen, see Paracetamol)							
Acetylsalicylic acid + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	67
Aminophenazone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Bucetine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Caffeine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
(Dipyrone, see Metamizol)							
Ethenzamide + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Isopyrine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Lactylphenethidine + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Metamizol + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Morazone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Nifenazone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Paracetamol + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Phenacetin + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Phenazone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Propyphenazone + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Salicylamide + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40

[a] Testing confirmed that the packed column described in the paper cited can be replaced by the given FSC HP-1 [66,67]. The given retention indices correspond to those measured on the FSC [67,68].

TABLE II

GC–MS PROCEDURES FOR THE IDENTIFICATION OF H_1-RECEPTOR BLOCKERS AND THEIR METABOLITIES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Adeptolon + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		30
Alimemazine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	28
Antazoline + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		30
Azatadine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		31
Bamipine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Benzquinamide + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		31
Brompheniramine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	31
Buclizine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Carbinoxamine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	29
Chlorbenzoxamine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	29
Chlorcyclizine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Chloropyramine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		30
Chlorphen(ir)amine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	31
Chlorphenoxamine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		29
Cinnarizine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Clemastine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	29
Clemizole + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Cyclizine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Cyproheptadine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	31
Dimetindene + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	31
Dimetotiazine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		28
Diphenhydramine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	29

Diphenylpyraline + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	29
Doxylamine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	29
Etodroxizine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Histapyrrodine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		30
Hydroxyzine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Isothipendyl + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	28
Ketotifen + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	31
Mebhydroline + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		31
Mecloxamine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		29
Meclozine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Medrylamine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		29
Mepyramine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30
Mequitazine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	28
Orphenadrine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	29
Oxatomide + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		30
Oxomemazine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	28
Phenindamine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		31
Pheniramine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	31
Phenyltoloxamine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	29
Promethazine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	28
(Pyrilamine, see Mepyramine)							
Pyrrobutamine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		31
Terfenadine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	31
Thiethylperazine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		28
Tolpropamine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		31
Trifluprornazine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	28
Tripelennamine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	30

TABLE 12

GC–MS PROCEDURES FOR THE IDENTIFICATION OF ANTIPARKINSONIAN DRUGS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Amantadine	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	34
Benzatropine[a]	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	34
Biperiden + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	34
Bornaprine + M	U (rat)	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS		34
Memantine + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	34
Metixene + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	34
Phenglutarimide + M	U (rat)	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS		34
Pridinol + M	U (rat)	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS		34
Procyclidine	U (rat)	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS		34
Profenamine + M	U (rat)	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS		34
Selegiline-M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	10 ng/ml	66,67
Selegiline-M	U	LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	10 ng/ml	76
Selegiline-M[c]	U	LLE, TPC	FSC HP-1 (190°C)	EI, scan	RI, MS	100 ng/ml	75,76
Tiapride + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	34
Trihexyphenidyl + M	U	HY, LLE, AC	FSC HP-1[b] (100–310/30°C)	EI, scan	RI, MS	th. conc.	34

[a] This compound is destroyed during acid hydrolysis. It can only be detected in a direct extract of urine [6].

[b] Testing confirmed that the packed column described in the paper cited can be replaced by the given FSC HP-1 [66,67]. The given retention indices correspond to those measured on the FSC [67,68].

[c] This enantioselective GC–MS procedure allows the differentiation between the (*R*)-(−)- and (*S*)-(+)-enantiomers of amphetamine and metamphetamine.

liquid extraction and C_{18} extraction. Leloux *et al.* [45] studied the effectiveness of three derivatization procedures: trifluoroacetylation of the amino group and trimethylsilylation of the hydroxy group, two-fold trifluoroacetylation and *n*-butylboronylation to form a cyclic boronate. The combination of N-trifluoroacetylation with O-trimethylsilylation was the best procedure. The mass spectra and structures of derivatized propranolol are shown in Fig. 2. The authors used an ion-trap mass spectrometer. The molecular ion is augmented by 1 u caused by self-ionization in the ion trap [89] (Fig. 2, bottom). The correct mass spectrum of *n*-butylboronated propranolol is shown in ref. 90. Hence it follows that it is risky to use fragment ions recommended for screening without reconsideration if quadrupole or magnetic sector analyzers were employed. The paper by Rofi and Aldoma [91] is useless for toxicology, as only data that were recorded using pure substances with no association with biosamples were published. Further chromatographic procedures were reviewed by Davies [92].

2.13. Antiarrhythmics (class I and IV)

Antiarrhythmics may lead to severe cardiac and central nervous disorders if overdosed. As the symptoms of such overdosing are similar to those of intoxication with other drugs or to symptoms of internal or neurological diseases, a toxicological analysis may be of great importance for diagnosis. Before determination in plasma, the drug must first be identified, preferably within a systematic screening procedure as described by Maurer [27] (Table 14).

2.14. Diuretics

Diuretics are misused and abused mainly in attempts to reduce body weight. The resulting hypokalaemia may lead to severe cardiac disorders. Toxicological screening for diuretics should be performed before extensive diagnostic work is begun. Diuretics are also misused in sports and, therefore, they have been banned by the IOC. For both indications GC–MS procedures have been published (Table 15). Lisi *et al.* [93] described an interesting GC–MS procedure after extractive methylation for the rapid and sensitive confirmation of an abuse of diuretics. They studied the effectiveness of toluene and dichloromethane as solvents for methyl iodide and of tetrabutylammonium ion (TBA), tetrapentylammonium ion (TPA) and tetrahexylammonium ion (THA) as phase-transfer reagents. As shown in Fig. 3, the use of methyl iodide dissolved in toluene and THA as counter ion (3) was more effective than TBA (1) and TPA (2). Park *et al.* [94], Maurer and Hausmann [95] and Gradeen *et al.* [96] described the identification of diuretics after extraction followed by methylation.

2.15. Laxatives

Abuse of laxatives may lead to serious disorders such as hypokalaemia, chronic diarrhoea or anorexia nervosa. Toxicological screening should be performed before extensive diagnostic work is started. Two GC–MS procedures were described (Table 16). The method of Kok and Faber [97] has the advantage that dioxyanthraquinone could be detected. The method of Maurer [26] is advantageous, because it is integrated in a systematic screening procedure for several classes of drugs (see Section 3). For the detection of the anthraquinone glycosides, which could not be found by GC–MS, a simple and rapid high-performance thin-layer chromatographic (HPTLC) method was developed [98].

3. SYSTEMATIC TOXICOLOGICAL ANALYSIS OF SEVERAL CLASSES OF DRUGS AND THEIR METABOLITES BY GC–MS ("GENERAL UNKNOWN ANALYSIS")

Clinical toxicological analysis is usually a single analysis which must be available around the clock. The method should be as rapid and precise as necessary for clinical diagnosis and therapy. Ideally, a single procedure should allow the detection of nearly all relevant toxicants. Similar problems arise in forensic toxicology. Because of the serious legal consequences, forensic toxicological analysis also has to be of high precision.

TABLE 13

GC–MS PROCEDURES FOR THE IDENTIFICATION OF β-BLOCKERS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Acebutolol	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Acebutolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Acebutolol	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Alprenolol + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	?	33
Alprenolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Alprenolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Alprenolol + M	U	EN, SPE, TFA	FSC CP-Sil-5-CB (140–280/5°C)	EI, SIM	RT, FI	10 ng/ml	86
Alprenolol + M	U	EN, LLE or SPE, TFA	FSC CP-Sil-5-CB (140–280/10°C)	EI, SIM	RT, FI	4–6 ng/ml	87
Alprenolol	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Atenolol[a]	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Atenolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Atenolol	U	EN, SPE, TFA	FSC CP-Sil-5-CB (140–280/5°C)	EI, SIM	RT, FI	10 ng/ml	86
Atenolol	U	EN, LLE or SPE, TFA	FSC CP-Sil-5-CB (140–280/10°C)	EI, SIM	RT, FI	4–15 ng/ml	87
Atenolol[a]	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Betaxolol + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	?	33
Betaxolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Betaxolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Bevantolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Bisoprolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Bisoprolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Bufuralol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Bunitrolol + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	?	33
Bupranolol + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Carazolol[a]	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	?	33
Carteolol + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Labetalol + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Labetalol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Labetalol	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Levobunolol	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Mepindolol[a]	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	?	33
Metipranol + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	?	33
Metoprolol + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33

Metoprolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Metoprolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Metoprolol + M	U	EN, SPE, TFA	FSC CP-Sil-5-CB (140–280/5°C)	EI, SIM	RT, FI	20 ng/ml	86
Metoprolol	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Metoprolol + M	U	EN, LLE or SPE, TFA	FSC CP-Sil-5-CB (140–280/10°C)	EI, SIM	RT, FI	6–10 ng/ml	87
Nadolol	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Nadolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Nadolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Nadolol	U	HY, LLE, (TFA +) TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Nifenalol	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33,67
Oxprenolol + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Oxprenolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Oxprenolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Oxprenolol + M	U	EN, SPE, TFA	FSC CP-SiL-5-CB (140–280/5°C)	EI, SIM	RT, FI	20 ng/ml	86
Oxprenolol	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°)	EI, scan	FI	?	72
Oxprenolol + M	U	EN, LLE or SPE, TFA	FSC CP-Sil-5-CB (140–280/10°C)	EI, SIM	RT, FI	10–15 ng/ml	87
Penbutolol + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Penbutolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Penbutolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Pindolol[a]	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Pindolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Pindolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Pindolol	U	EN, SPE, TFA	FSC CP-Sil-5-CB (140–280/5°C)	EI, SIM	RT, FI	20 ng/ml	86
Pindolol	U	EN, LLE or SPE, TFA	FSC CP-Sil-5-CB (140–280/10°C)	EI, SIM	RT, FI	10–15 ng/ml	87
Propafenone + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Propranolol + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Propranolol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Propranolol + M	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI/CI, scan/SIM	RT, FI	20 ng/ml	88
Propranolol	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Propranolol + M	U	EN, SPE, TFA	FSC CP-Sil-5-CB (140–280/5°C)	EI, SIM	RT, FI	10 ng/ml	86
Propranolol + M	U	EN, LLE or SPE, TFA	FSC CP-Sil-5-CB (140–280/10°C)	EI, SIM	RT, FI	4–6 ng/ml	87
Sotalol	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Sotalol	U	EN, SPE, TFA + TMS	FSC DB-1 (90–260/40°C)	EI, scan	RT, FI	th. conc.	45
Sotalol	U	HY, LLE, TFA + TMS	FSC SE-30 (160–300/20°C)	EI, scan	FI	?	72
Timolol + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	?	33
Toliprolol + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	?	33

[a] These compounds are destroyed during acid hydrolysis. They can only be detected in a direct extract of urine [6].

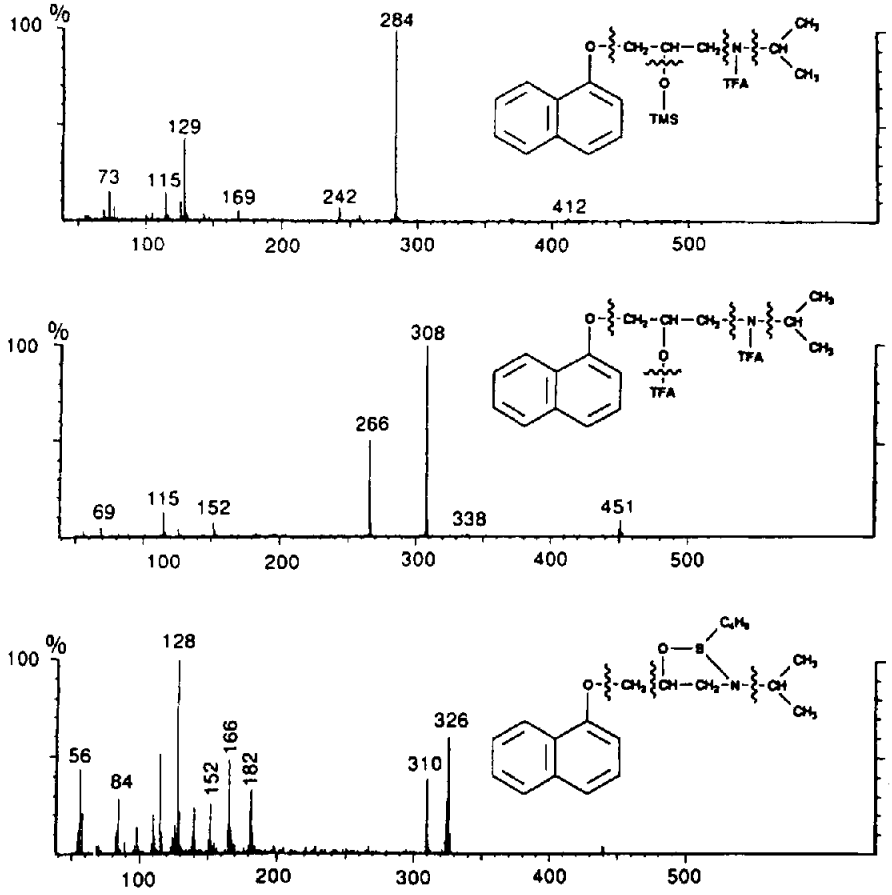

Fig. 2. Mass spectra and structures of derivatized propranolol (top, N-trifluoroacetylation and O-trimethylsilylation; middle, two-fold trifluoroacetylation; bottom, *n*-butylboronylation to form a cyclic boronate) [45]. Details of the method are summarized in Table 13.

The first step in the toxicological analysis is the identification of the usually unknown drugs and poisons in body fluids. Several problems result from the so-called "general unknown analysis". There are thousands of drugs and poisons which could have been taken, and each compound may form several metabolites, complicating the identification. Some substances are completely metabolized and so the can only be identified in plasma or urine by their metabolites. On the other hand, all metabolites must be differentiated from other potential poisons. Often low substance concentrations must be detected. Further, all exogenous substances must be separated and differentiated from endogenous biological substances. Finally, the results must be available as rapidly as possible so that a specific therapy can be initiated.

For these reasons a systematic toxicological analysis procedure is necessary that allows the simultaneous detection of as many toxicants as possible in biosamples. In the author's experience, unspecific chromatographic methods, even if several are combined [99], are not sufficient for these purposes, because the same chromatographic behaviour is not evident for the identity of two compounds [100]. Finally, all chromatographic peaks or spots have to be identified because any of them may represent a potential poison. A "general unknown analysis" procedure using GC–MS was developed that allows the simultaneous screening and confirmation of the

TABLE 14

GC–MS PROCEDURES FOR THE IDENTIFICATION OF ANTIARRHYTHMICS (CLASS I AND IV) AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Ajmaline + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Aprindine + M	U (rat)	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS		27
Diltiazem + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Disopyramide + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Flecainide + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Gallopamil + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Lidocaine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Lorcainide + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Mexiletine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Phenytoin + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Prajmaline + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Propafenone + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Quinidine + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Sparteine[a] + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Tocainide + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Verapamil + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27

[a] This compound is destroyed during acid hydrolysis. It can only be detected in a direct extract of urine [6].

TABLE 15

GC–MS PROCEDURES FOR THE IDENTIFICATION OF DIURETICS AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Acetazolamide	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Acetazolamide	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Bendroflumethiazide	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Bendroflumethiazide	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Bumetanide	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Bumetanide	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Bumetanide	U	LLE + ME	FSC DB-1 (80–300/30/10°C)	EI, scan	MS	?	96
Canrenone	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Canrenone	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Cyclopenthiazide	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Chlorthalidone	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Chlorthalidone	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Chlorothiazide	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Dichlorphenamide	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Ethacrynic acid	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Ethacrynic acid	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Furosemide	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Furosemide	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Furosemide	U	LLE, ME	FSC HP-1 (100–310/30°C)	EI, scan	FI	th. conc.	95
Hydrochlorothiazide	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Hydrochlorothiazide	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Hydrochlorothiazide	U	LLE, ME	FSC HP-1 (100–310/30°C)	EI, scan	FI	th. conc.	95
Hydroflumethiazide	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Mefruside	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Mefruside	U	LLE, ME	FSC HP-1 (100–310/30°C)	EI, scan	FI	th. conc.	95
Metolazone	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Piretanide	U	LLE, ME	FSC HP-1 (10–310/30°C)	EI, scan	FI	th. conc.	95
Probenecid	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Quinethazone	U	LLE + ME[a]	FSC HP-Ultra 1 (130–320/40°C)	EI, SIM	RT, FI	30–100 ng/ml	93
Triamterene	U	SPE, ME	FSC SE-30 (200–300/15/10°C)	EI, scan	RT, FI	th. conc.	94
Xipamide	U	LLE, ME	FSC HP-1 (100–310/30°C)	EI, scan	FI	th. conc.	95

[a] Extractive methylation by methyl iodide in toluene using tetrahexylammonium ions as phase-transfer reagent.

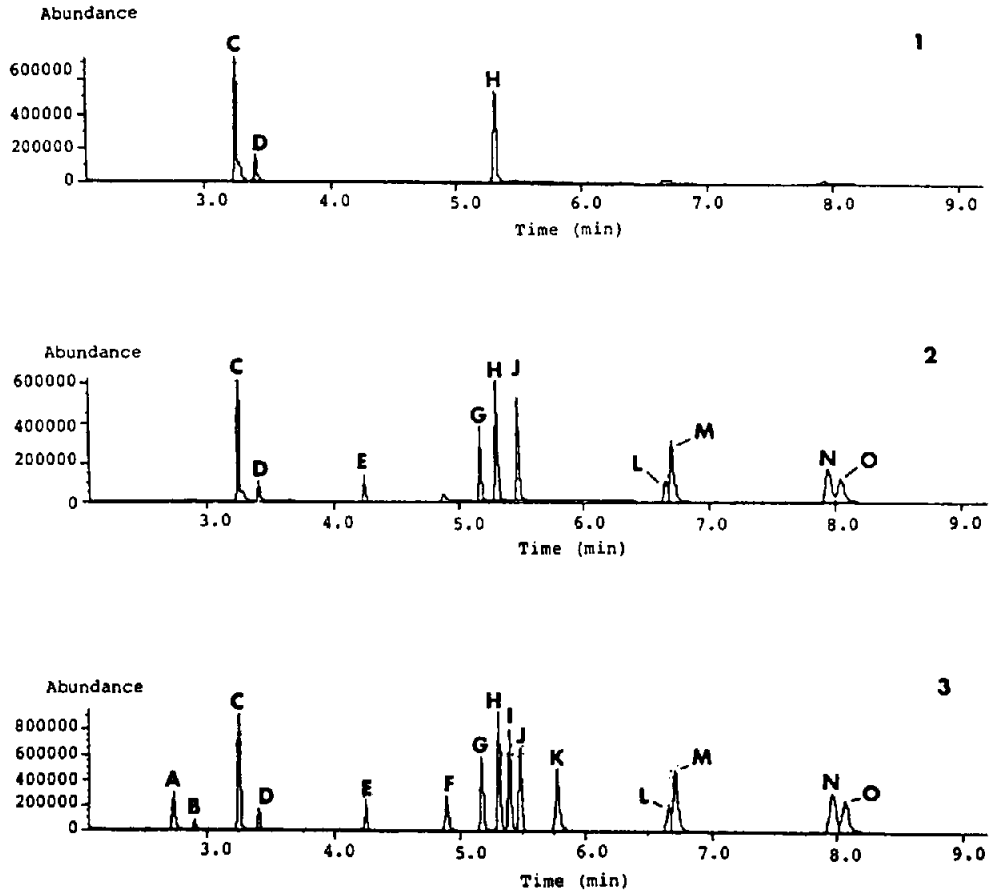

Fig. 3. Chromatograms (SIM) of diuretics extracted and derivatized by extractive methylation using methyl iodide in toluene and (1) tetrabutylammonium ion, (2) tetrapentylammonium ion and (3) tetrahexylammonium ion as counter ion [84]. Peaks: A = monomethylated acetazolamide; B = trimethylated acetazolamide; C = monomethylated probenecid; D = monomethylated ethacrynic acid; E = tetramethylated dichlorphenamide; F = trimethylated chlorothiazide and tetramethylated hydroflumethiazide; G = trimethylated furosemide; H = dimethylated mefruside (internal standard); I = tetramethylated chlorthalidone; J = trimethylated bumetanide; K = tetramethylated hydrochlorothiazide and tetramethylated quinethazone; L = canrenone; M = tetramethylated bendroflumethiazide; N = trimethylated metolazone; O = tetramethylated cyclopenthiazide. Details of the method are summarized in Table 15.

following categories of drugs: barbiturates and other sedative–hypnotics, anticonvulsants, benzodiazepines, antidepressants, phenothiazine and butyrophenone neuroleptics, opioid and other potent analgesics, non-opioid analgesics, antihistamines, antiparkinsonian drugs, β-blockers, antiarrhythmics, diphenol laxatives and their metabolites (Table 17, and references cited therein). The screening is performed using reconstructed mass chromatograms which may indicate the presence of suspected mass spectra in the full mass spectra stored during GC analysis. Positive signals can be confirmed by visual or computerized comparison of the peaks underlying full mass spectra with reference spectra [67,101]. Eight ions per category were individually selected from the mass spectra of the corresponding drugs and their metabolites identified in authentic urine samples (Table 18). These groups of fragment ions were named computer monitoring programs. As some fragment ions were typical for different categories, reduced monitoring programs were recommended for general unknown analysis (Table 19) [25,66]. Using these programs

TABLE 16

GC–MS PROCEDURES FOR THE IDENTIFICATION OF LAXATIVES AND THEIR METABOLITES IN BIOSAMPLES

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Bisacodyl + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	FI	50 ng/ml	26
Bisacodyl − M	U	EN, SPE, TMS	3.8% SE-30 (280°C)	EI, scan	MS	10 ng/ml	97
Dioxyanthraquinone	U	EN, SPE, TMS	3.8% SE-30 (280°C)	EI, scan	MS	10 ng/ml	97
Oxyphenisatin	U	EN, SPE, TMS	3.8% SE-30 (280°C)	EI, scan	MS	50 ng/ml	97
Phenolphthalein + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	FI	50 ng/ml	26
Phenolphthalein	U	EN, SPE, TMS	3.8% SE-30 (280°C)	EI, scan	MS	30 ng/ml	97
Picosulphate + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	FI	50 ng/ml	26

TABLE 17

SYSTEMATIC TOXICOLOGICAL ANALYSIS OF SEVERAL CLASSES OF DRUGS AND THEIR METABOLITES ("GENERAL UNKNOWN ANALYSIS")

Drug	Sample	Work-up	Column	Detection mode	Reference data	Detection limit	Ref.
Barbiturates + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	23
Anticonvulsants + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	24
Benzodiazepines + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	32
Antidepressants + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	35
Neuroleptics + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	38
Butyrophenones + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	39
Opioid analgesics + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	37
Non-opioid analgesics + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	40
Antihistamines + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	28–31
Antiparkinsonians + M	U	HY, LLE, AC	FSC HP-1[a] (100–310/30°C)	EI, scan	RI, MS	th. conc.	34
β-Blockers + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	33
Antiarrhythmics + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	RI, MS	th. conc.	27
Laxatives + M	U	HY, LLE, AC	FSC HP-1 (100–310/30°C)	EI, scan	FI	th. conc.	26

[a] Testing confirmed that the packed column described in the paper cited can be replaced by the FSC HP-1 [66,67]. The given retention indices correspond to those measured on the FSC [67,68].

TABLE 18

COMPUTER MONITORING PROGRAMS FOR SCREENING FOR PARTICULAR CATEGORIES OF DRUGS AND THEIR METABOLITES

Category of drugs	Selective fragment ions (*m/z*)	Ref.
Barbiturates and other sedative–hypnotics	83, 117, 141, 167, 169, 207, 211, 235	23
Anticonvulsants	58, 104, 113, 117, 165, 193, 204, 246	24
Benzodiazepines	205, 211, 230, 241, 245, 249, 312, 333	32
Antidepressants, neuroleptics I	58, 72, 86, 100, 114, 141, 193, 194	35,38
Antidepressants, neuroleptics II	98, 132, 154, 191, 198, 205, 243, 267	35,38
Butyrophenones	112, 123, 134, 189, 203, 223, 233, 287	39
Opioids, potent analgesics	69, 71, 87, 187, 242, 327, 341, 343	37
Non-opioid analgesics	109, 123, 137, 188, 245, 259, 288, 308	40
Phenothiazine antihistamines	58, 72, 100, 114, 124, 128, 141, 199	28
Alkanolamine antihistamines	58, 139, 165, 167, 179, 182, 218, 260	29
Ethylenediamine antihistamines	58, 72, 85, 125, 165, 183, 198, 201	30
Alkylamine antihistamines	58, 169, 203, 205, 230, 233, 262, 337	31
Antiparkinsonian drugs	86, 98, 136, 150, 165, 196, 197, 208	34
β-Blockers	72, 86, 98, 140, 151, 159, 200, 335	33
Antiarrhythmics	58, 72, 84, 86, 136, 224, 266, 426	27
Laxatives	349, 360, 361, 379, 390, 391, 402, 432	26

for mass chromatography, the presence of the above-mentioned drugs and/or their metabolites could be indicated. The identity of any of these compounds can be confirmed by visual or computerized comparison of the peaks underlying full mass spectra with reference spectra [67,101]. The procedure is presented in Fig. 4. At the top, a total ion chromatogram of a urine extract after acid hydrolysis and acetylation is shown, in the middle, selective mass chromatograms are shown indicating psychoactive drugs, antihistamines and some antiarrhythmics ("general unknown" computer-monitoring program 1, see Table 19), and at the bottom, the result of a computer library search [101] of the mass spectrum, which underlies the marked peak, is documented [25]. As shown, the marked peak could be identified as the acetylated O-desmethyl metabolite of the calcium channel blocker diltiazem. In the same run ten further drugs could be identified simultaneously.

This procedure allows the rapid and specific detection of most of the toxicologically relevant drugs in urine samples after therapeutic doses. Therefore, this procedure has proved to be suitable also for the screening of abused medicaments in psychiatry. After the unequivocal identification, quantification of the drugs in plasma

TABLE 19

COMPUTER MONITORING PROGRAMS FOR GENERAL UNKNOWN ANALYSIS [25,66]

Computer monitoring program (CMP)	Fragment ions (*m/z*)
"General Unknown" CMP 1	58, 72, 86, 98, 100, 114, 128, 198
"General Unknown" CMP 2	205, 211, 230, 241, 245, 249, 312, 333
"General Unknown" CMP 3	112, 123, 134, 169, 191, 203, 223, 233
"General Unknown" CMP 4	69, 83, 104, 141, 154, 165, 167, 235
"General Unknown" CMP 5	71, 87, 109, 188, 193, 327, 343, 371
"General Unknown" CMP 6	84, 136, 159, 182, 224, 266, 337, 426

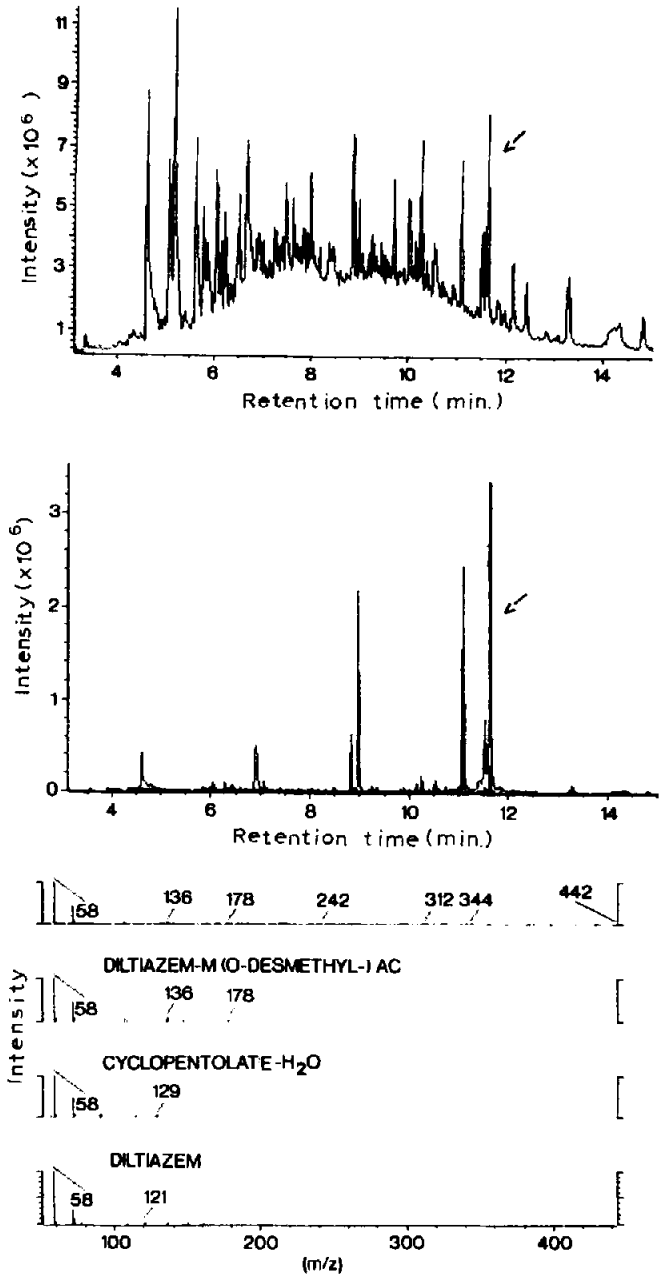

Fig. 4. (Top) total ion chromatogram of a urine extract after acid hydrolysis and acetylation, (middle) selective mass chromatograms indicating psychoactive drugs, antihistamines and some antiarrhythmics ("general unknown" computer monitoring program 1, see Table 19) and (bottom) result of a computer library search [101] of the mass spectrum underlying the marked peak [25]. Details of the method are described in Section 3 and summarized in Table 17.

can be performed by immunological or chromatographic methods, preferably by GC–MS using stable isotopes as internal standards.

4. CONCLUSIONS

In the last ten years, many papers have appeared concerning the GC–MS detection of un-

known drugs and their metabolites in biosamples relevant to clinical toxicology, forensic toxicology and doping control. They describe either procedures for confirmation or chromatographic or immunological results or for systematic toxicological analysis. Confirmation was usually performed in the SIM mode, because only a particular compound had to be identified. As inexpensive mass spectrometers are widely available today, many papers have appeared in the last few years in this field, mostly improving preceding papers. Unfortunately, the titles of some papers indicate GC–MS procedures, but no GC–MS data are given with the exception of the apparatus data and a stereotyped sentence in the Conclusion section such as "The (chromatographic or immunological) results could be confirmed by GC–MS" [47,77,78,102,103]. Further, some papers on toxicological analysis contain only data on pure reference substances [50–55,90,91]. In the author's experience, detection limits are only useful if they were measured using spiked biosamples and if the drug itself is the predominant compound in the sample. In many instances the metabolites can be detected at higher concentrations and for a longer time.

GC–MS is today the method of choice for systematic toxicological analysis in clinical and forensic toxicology. If the drug is unknown, the full-scan mode is the method of choice, as comparison of the full mass spectra with reference spectra is necessary. The screening can be performed using mass chromatography followed by a library search. As negative results are very rare in clinical toxicology, in contrast to drug testing or doping control, most of the results have to be confirmed. In the author's opinion, pre-selection by thin-layer chromatography, GC and/or high-performance liquid chromatography is very time-consuming and expensive, if the staff costs are considered. The earlier argument that GC–MS is too expensive and complicated is not longer up-to-date.

5. PERSPECTIVES OF GC–MS IN ANALYTICAL TOXICOLOGY

GC–MS is the most powerful method in analytical toxicology today. This review documents its wide use in science and practice. As pharmacologists develop increasingly highly selective and therefore low-dosed drugs, the sensitivity of conventional GC MS will no longer be sufficient. NICI of compounds with electronegative sides or of compounds derivatized with reagents containing such sides will perhaps be the method in future. Unfortunately, the costs are still relatively high for this ionization technique. The coupling of liquid chromatography with MS has been continuously improved. This method will allow in the future the precise detection of toxicologically relevant compounds which are not volatile in GC.

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