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Toxicological detection of the new designer drug 1-(4-methoxyphenyl)piperazine and its metabolites in urine and differentiation from an intake of structurally related medicaments using gas chromatography–mass spectrometry☆

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Abstract

Studies are described on the toxicological analysis of the piperazine-derived designer drug 1-(4-methoxyphenyl)piperazine (MeOPP) in rat urine using gas chromatography–mass spectrometry (GC–MS). The authors' systematic toxicological analysis (STA) procedure using full-scan GC–MS after acid hydrolysis, liquid–liquid extraction and microwave-assisted acetylation allowed the detection of MeOPP and its metabolites 1-(4-hydroxy phenyl)piperazine and 4-hydroxyaniline in rat urine after administration of a single dose corresponding to doses commonly taken by drug users. Therefore, this procedure should also be suitable for detection of a MeOPP intake in human urine. However, the metabolites of MeOPP are not unique and can be produced from other drugs. Therefore, differentiation of use of this designer drug from use of the medicaments dropropizine, oxypertine or others, which are metabolized to the MeOPP isomer 1-(2-methoxyphenyl)piperazine, is discussed.

Keywords: Designer drug; 1-(4-Methoxyphenyl)piperazine; Dropropizine; Oxypertine

1. Introduction

The illicit drug market for recreational drugs has changed considerably during the 1990s. Several new types of drugs have appeared and information about these drugs is readily available on the internet [2]. Piperazine-derived compounds like *N*-benzylpiperazine (BZP), 1-(3,4-methylenedioxybenzyl)piperazine (MDBP), 1-(4-methoxyphenyl)piperazine (MeOPP), 1-(3-trifluoromethylphenyl)piperazine (TFMPP) and 1-(3-chlorophenyl)piperazine (mCPP) are examples of these newer groups of designer drugs which are mentioned as psychoactive chemicals in "scene books" [3,4] as well as internet web sites (http://www.erowid.org, http://www.lycaeum.org). Seizures have been made throughout the world [5–14], and a fatality involving piperazine-derived compounds has already been reported [15]. The increasing abuse of BZP and TFMPP in the United States of America led to the temporary placement of these two compounds into Schedule I of the Controlled Substance Act [16].

Introduction of a methoxy moiety is a known structural variation of designer drugs of the amphetamine type. The corresponding 4-methoxy substituted piperazine derivative is MeOPP. So far, only little information is available about the pharmacological and toxicological properties of MeOPP. However, as other 1-arylpiperazines are known to show central serotonergic effects [17–21], it can be assumed that MeOPP shows similar effects.

MeOPP has been shown to be mainly metabolized by *O*-demethylation catalyzed by cytochrome P450 2D6 and by metabolic degradation of the piperazine heterocycle [22]. In a study on the metabolism of the cough suppressant dropropizine (DRO), the major MeOPP metabolite 1-(4-hydroxyphenyl)piperazine (4-HO-PP) has been identified to be also a common metabolite of this therapeutic drug [23]. Apart from DRO, there are several other 4-substituted arylpiperazine derivatives which are metabolized to the corresponding *N*-arylpiperazines, which might lead to

☆ Part of these results was reported at the 39th International TIAFT Meeting, Prague, 26–30 August 2001 [1].

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misinterpretation of analytical results if metabolites common with MeOPP are formed [24–26].

Screening for and validated quantification of MeOPP in human blood plasma has been published using GC–MS [27]. However, in clinical and forensic toxicology as well as in doping control, screening procedures in urine are necessary, because drugs or toxicants can be detected for several hours or even days after ingestion, in contrast to blood analysis which covers only a few hours [28,29]. Procedures for urinalysis of MeOPP have not yet been published.

The aim of the study presented here was to examine the detectability of MeOPP within the authors' systematic toxicological analysis (STA) procedure [6,30–32] in (rat) urine by GC–MS and how an intake can be differentiated from an intake of the substituted *N*-phenylpiperazines DRO and/or oxypertine (OX), an antipsychotic drug.

2. Experimental

2.1. Chemicals and reagents

MeOPP–2HCl, 4-HO-PP, 1-(2-methoxyphenyl)piperazine–HCl (2-MeOPP), 1-(2-hydroxyphenyl)piperazine (2-HO-PP) were obtained from Lancaster Synthesis, Mühlheim

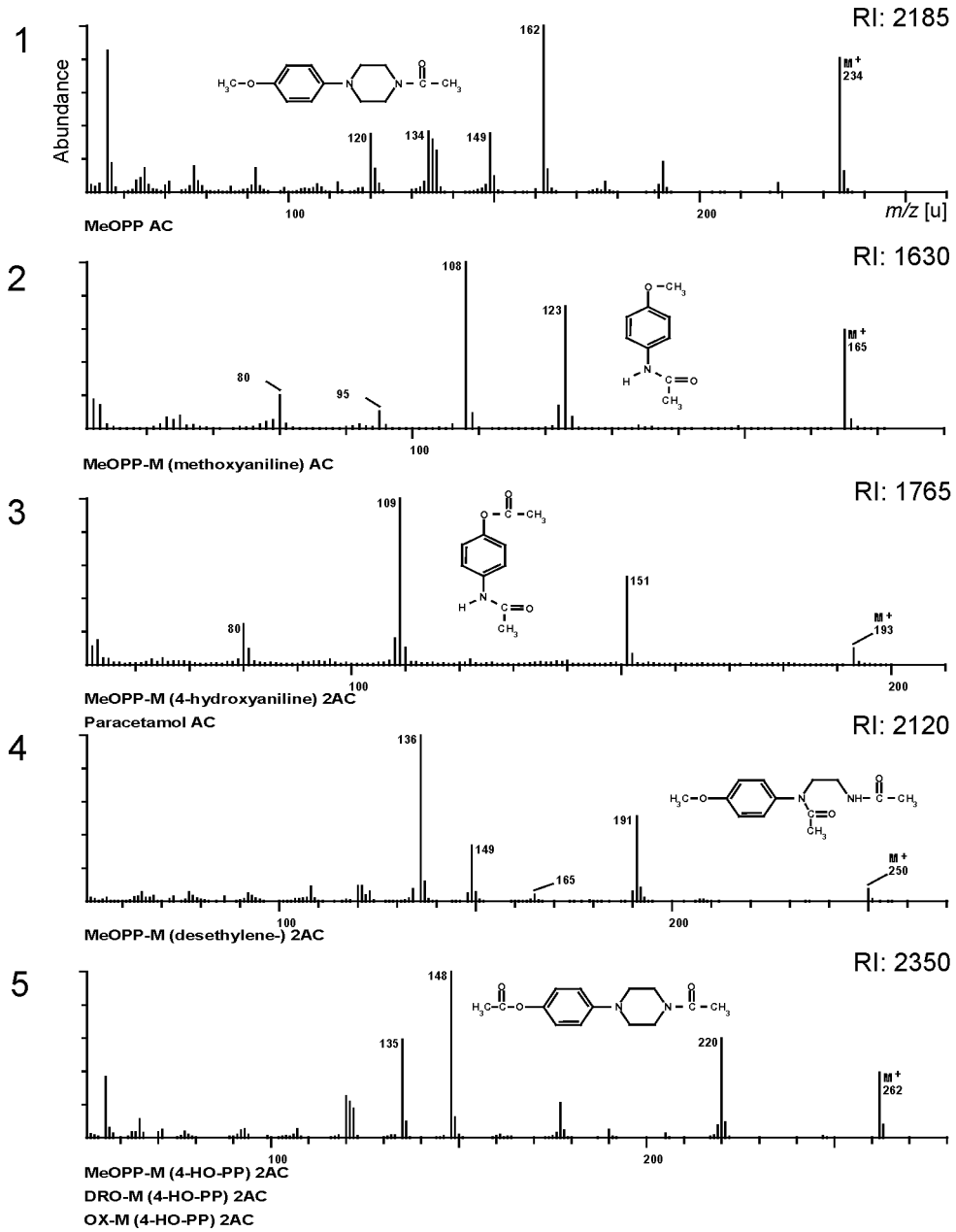

Fig. 1. EI mass spectra, the gas chromatographic retention indices (RI), and structures of MeOPP, DRO, OX and/or their metabolites as well as of 2-MeOPP and 2-HO-PP (after acetylation) needed for differentiation of an intake of MeOPP from an intake of DRO, OX or other substituted phenylpiperazines. Axes only labeled for spectrum no. 1.

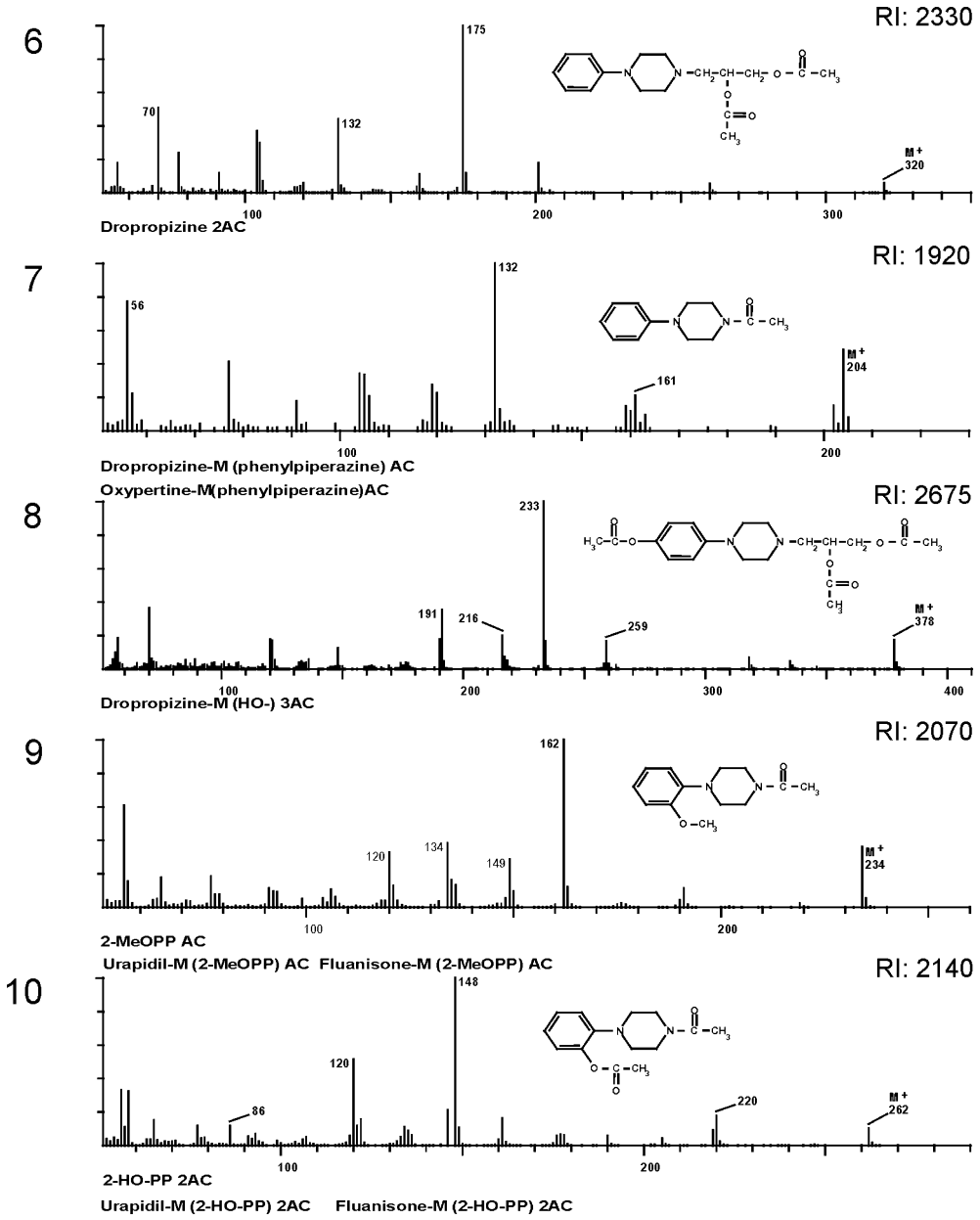

Fig. 1. (*Continued*).

(Germany); DRO was obtained from Sigma, Taufkirchen (Germany); oxypertine–HCl was kindly provided by Prof. K. Pfleger, Homburg. All other chemicals and biochemicals were obtained from E. Merck, Darmstadt (Germany) and were of analytical grade.

2.2. Urine samples

The investigations were performed using urine of male rats (Wistar, Ch. River, Sulzfleck, Germany) which had been administered a single of the following doses in aqueous solution by gastric intubation ($n = 2$ each): 1.0 mg/kg body mass (BM) dose of MeOPP, 1.3 mg/kg BM dose of DRO, 1.5 mg/kg BM dose of OX. These doses correspond to an estimated abusers' dose of MeOPP or to a therapeutic dose of DRO or OX. Urine was collected separately from the faeces over a 24 h period. All samples were directly worked up, derivatized, and analyzed by GC–MS as described below. Blank rat urine samples had been collected before drug administration to check whether the samples were free of interfering compounds. Authentic human urine samples after intake of DRO had been collected during a study on the metabolism of DRO [23].

2.3. Sample preparation for toxicological analysis

The urine samples (5 ml) were divided into two equal aliquots. One aliquot was refluxed with 1 ml of 37% hydrochloric acid for 15 min. Following hydrolysis, the sample was mixed with 2 ml of 2.3 mol/l aqueous ammonium sulfate

and 1.5 ml of 10 mol/l aqueous sodium hydroxide to obtain a pH value of 8–9. Before extraction, the other aliquot of unhydrolyzed urine was added and this solution was extracted with 5 ml of a dichloromethane–isopropanol–ethyl acetate mixture (1:1:3, v/v/v). After phase separation by centrifugation, the organic layer was transferred and carefully evaporated to dryness at 56 °C. The residue was derivatized by acetylation with 100 μl of an acetic anhydride–pyridine mixture (3:2, v/v) for 5 min under microwave irradiation at about 440 W [31]. After careful evaporation of the derivatization mixture, the residue was dissolved in 100 μl of methanol and 2 μl of this sample were injected into the GC–MS.

2.4. Gas chromatography–mass spectrometry

The drugs and their metabolites were separated and identified in derivatized urine extracts using a Hewlett-Packard (Agilent, Waldbronn, Germany) 5890 series II gas chromatograph combined with an HP 5989B MS engine mass spectrometer and an HP MS ChemStation (DOS series) with HP G1034C software. The GC conditions were as follows: splitless injection mode; column, HP-1 capillary (12 m × 0.2 mm i.d.), cross linked methyl silicone, 330 nm film thickness; injection port temperature, 280 °C; carrier gas, helium; flow-rate, 1 ml/min; column temperature, programmed from 100–310 °C at 30°/min, initial time 3 min, final time 8 min. The MS conditions were as follows: full scan mode: *m/z* 50–550; electron ionization (EI) mode: ionization energy, 70 eV; chemical ionization using methane, positive mode (PICI): ionization energy, 230 eV; ion source temperature, 220 °C; capillary direct interface heated at 260 °C.

For toxicological analysis of MeOPP and its metabolites, mass chromatography with the selected ions *m/z* 109, 148, 151, 162, 234, and 262 was used. These ions were selected from the corresponding mass spectra (Fig. 1). The identity of the peaks in the mass chromatograms was confirmed by computerized comparison of the mass spectra underlying the peaks (after background subtraction) with the reference spectra [33].

3. Results and discussion

3.1. Sample preparation

Cleavage of glucuronide and/or sulfate conjugates was necessary before extraction because those would not be

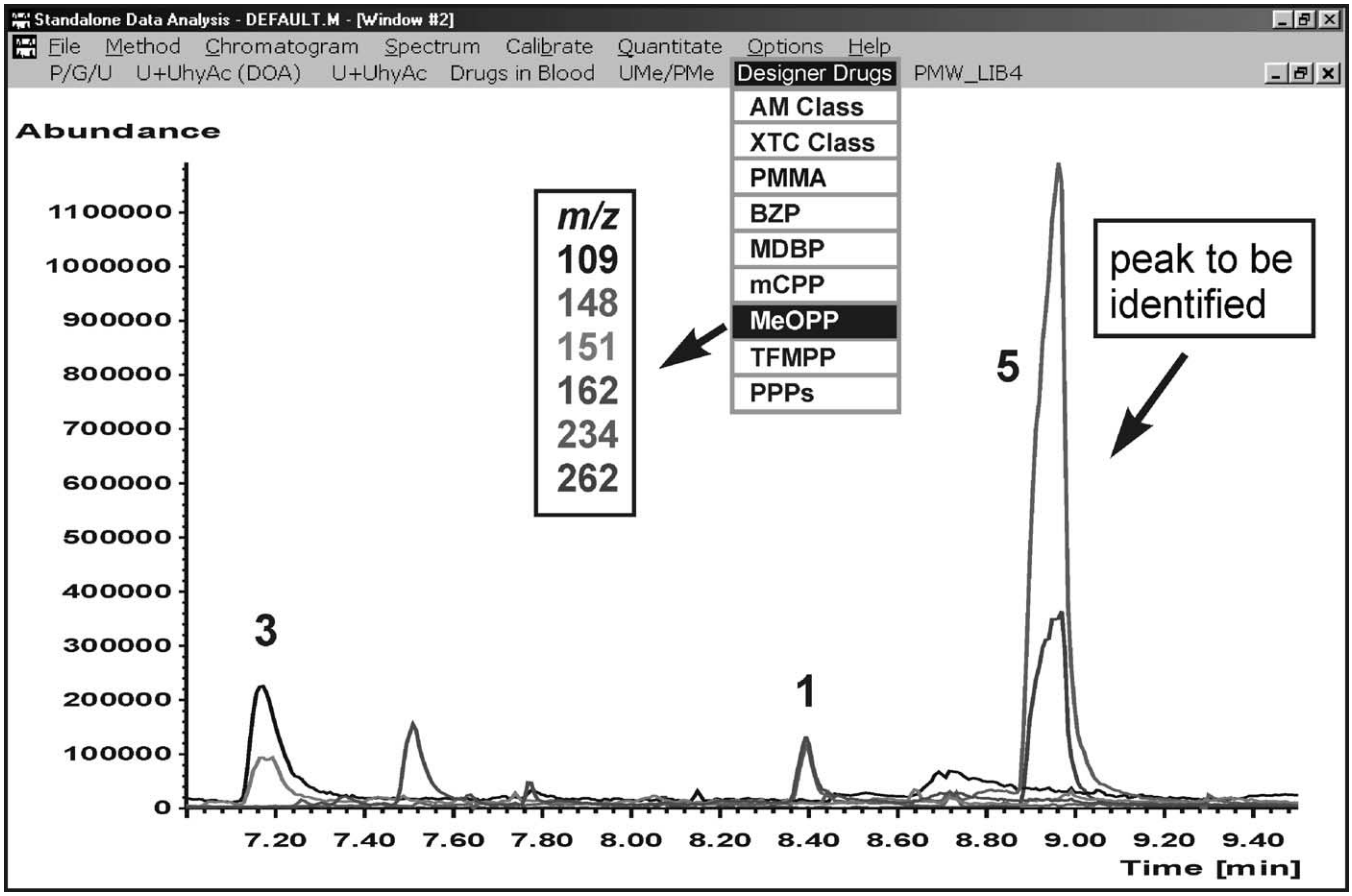

Fig. 2. Typical reconstructed mass chromatograms with the given ions of an acetylated extract of a rat urine sample collected over 24 h after application of a common abuser's dose of 1.0 mg/kg BM of MeOPP indicating the presence of MeOPP (peak no. 1) and its metabolites 4-hydroxyaniline (peak no. 3) and 4-HO-PP (peak no. 5). The peak numbers correspond to those used in Fig. 1.

extracted by the applied procedure. Acid hydrolysis has proven to be very efficient and fast for cleavage of conjugates [28]. However, some compounds were found to be altered or destroyed during hydrolysis [31,32]. Therefore, one of the two equal urine aliquots was left unhydrolyzed and added to the hydrolyzed one before extraction. This modified sample preparation was a compromise between the necessity of a quick cleavage of conjugates and the detectability of compounds destroyed during acid hydrolysis. Although the modification of the STA procedure led to lower extract concentrations of compounds excreted in conjugated form, this modified procedure was sufficient, because of the high sensitivity of modern GC–MS apparatus [31,32].

The samples were extracted at pH 8–9, because metabolic formation of aromatic hydroxy groups may lead to phenol bases which are best extracted at this pH. Using a more alkaline pH for extraction leads to decreased extraction efficacies of such compounds. Further, these metabolites may be excreted for a longer period of time than the parent compounds [23,34–39]. Derivatization of the extracts was indispensable for sensitive detection due to improved GC properties. The extraction efficacy determined for MeOPP after STA working-up was 88 ± 15% ($n = 5$) at 1000 ng/ml, and for *para*-hydroxy-*N*-phenylpiperazine 42 ± 11% ($n = 5$) at 1000 ng/ml.

3.2. Detection of MeOPP and its metabolites by GC–MS

MeOPP and its metabolites were separated by GC and identified by EI MS after acid hydrolysis, extraction and acetylation. Fig. 1 shows the EI spectra, the structures and the retention indices (RIs) of the acetylated compounds and their unique metabolites (for comparison: the RIs of acetylated amphetamine and methylenedioxymethamphetamine were 1505 and 2140, respectively). The RIs provide preliminary indications and may be useful to gas chromatographers without a GC–MS facility. The RIs were recorded during the GC–MS procedure and calculated in correlation with the Kovats' indices [40] of the components of a standard solution of typical drugs which is measured daily for testing the GC–MS performance [41,42]. The reproducibility of RIs measured on capillary columns was better using a mixture of drugs than that of the homologous hydrocarbons recommended by Kovats.

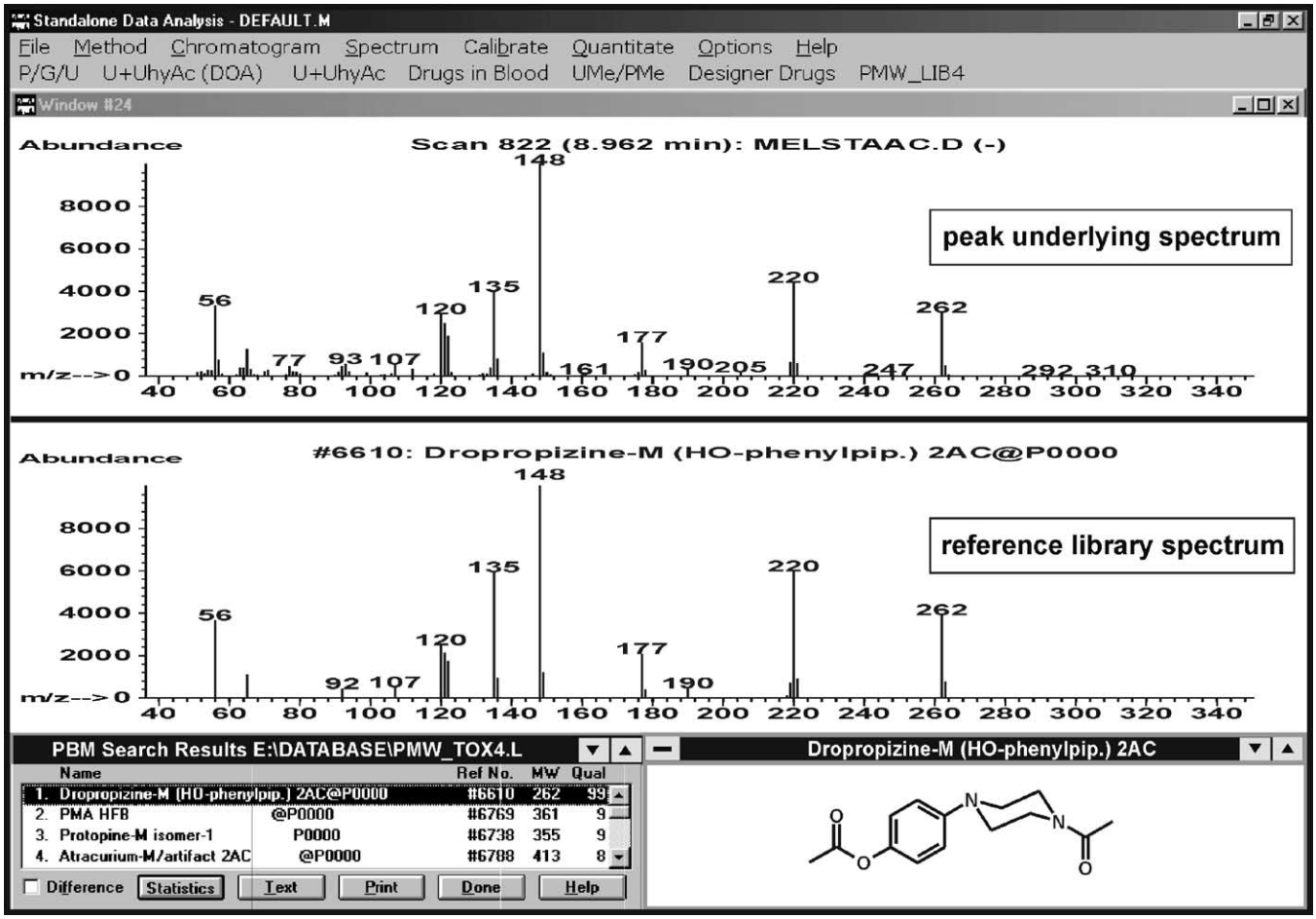

Fig. 3. Mass spectrum underlying the indicated peak in Fig. 2, the reference spectrum, the structure, and the hit list found by computer library search.

Mass chromatography with the selected ions *m*/*z* 109, 148, 151, 162, 234, and 262 was used to indicate the presence of MeOPP and/or its metabolites. Fig. 2 shows typical reconstructed mass chromatograms of the above mentioned ions of an acetylated extract of a rat urine sample taken after administration of 1.0 mg/kg BM of MeOPP. The peak numbers correspond to the numbering in Fig. 1. The identity of peaks in the mass chromatograms was confirmed by computerized comparison of the underlying mass spectrum with reference spectra [33]. The ions *m*/*z* 162 and 234 were used for indication of the presence of the parent compound MeOPP, the ions *m*/*z* 148 and 262 for the major metabolite 4-HO-PP, and the ions *m*/*z* 109 and 151 for the further metabolite 4-hydroxyaniline. Screening for the other metabolites was not useful, since they were only excreted in minor amounts and could only be detected after application of higher doses of MeOPP [22].

As illustrated in Fig. 3, the identity of the marked peak in the mass chromatograms was confirmed by computerized comparison of the underlying mass spectrum with reference spectra recorded during this study. As 4-HO-PP is also a metabolite of DRO, the library labeled this spectrum as a DRO metabolite. In order to avoid misinterpretation of the mass spectral analysis, proper use of the Pfleger/Maurer/Weber library [33] is indispensable. The "@"sign indicates that the compound can also be found after intake of other compounds given in the corresponding handbooks [43,44].

Interferences by biomolecules or further drugs indicated in the reconstructed mass chromatograms could be excluded, because these compounds have different gas chromatographic and/or mass spectral properties. The corresponding RIs and reference mass spectra are included in the used reference library.

The authors' STA procedure allowed unambiguous identification of MeOPP and its metabolites in rat urine after administration of a dose corresponding to a common drug users' dose to rats. Previous studies on the metabolism of MeOPP showed that MeOPP is extensively metabolized and therefore, a urine screening should also be focussed on the metabolites with 4-HO-PP as target analyte. The limit of detection was measured under routine GC–MS conditions for MeOPP to be 50 ng/ml of urine (signal-to-noise $S/N > 3$) and for 4-HO-PP 100 ng/ml of urine ($S/N > 3$). Finally, it could be shown that an intake of a dose of MeOPP that corresponds to a common drug users' dose could be detected in rat urine.

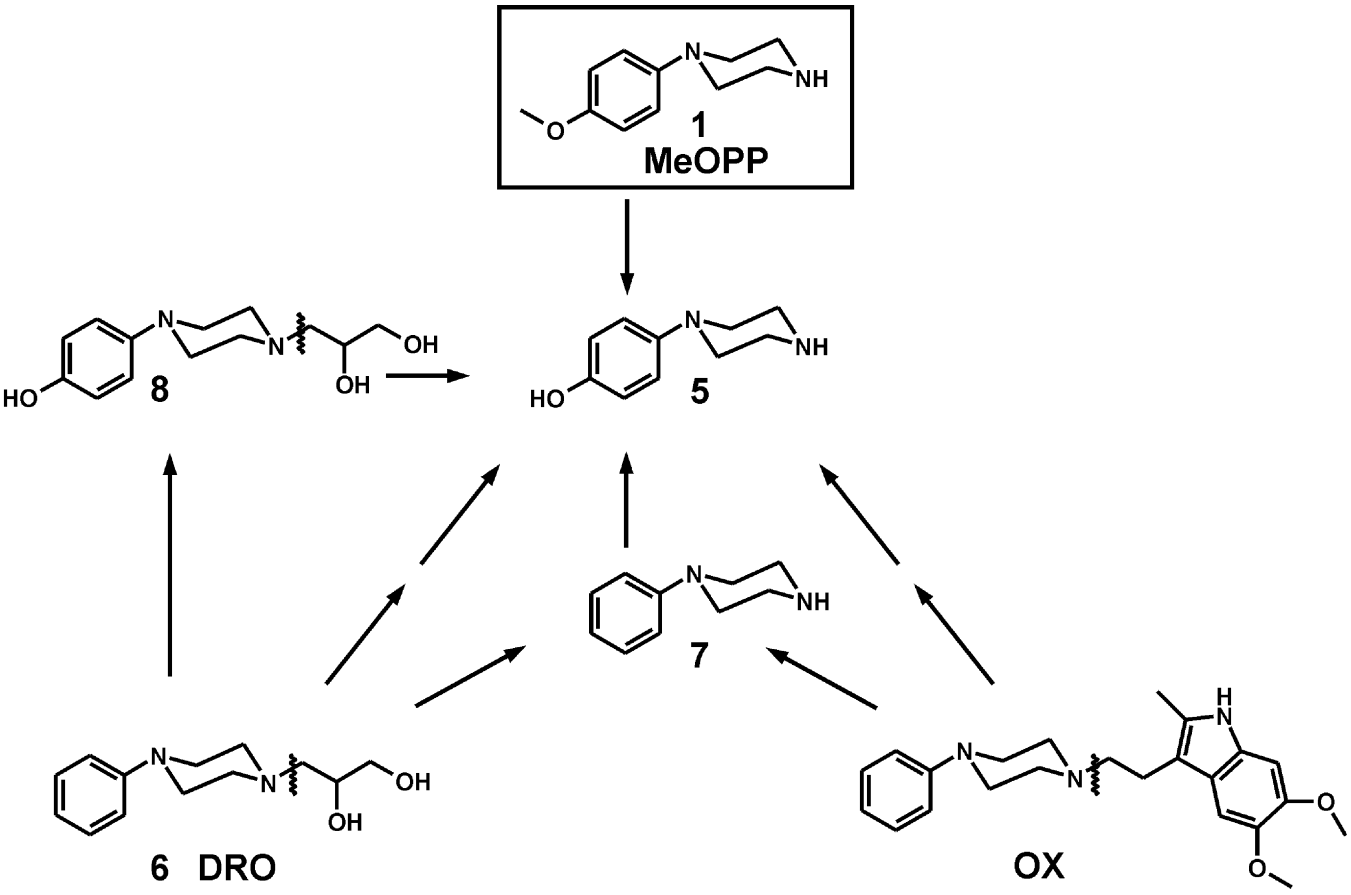

Fig. 4. Part of the metabolic pathways of MeOPP, DRO and OX relevant for detection and differentiation of these drugs in urine within the STA. The numbers correspond to those used in Fig. 1.

3.3. Differentiation of an MeOPP intake from an intake of structurally related compounds

There are several 4-substituted arylpiperazines which have been reported to be metabolized to the corresponding 1-arylpiperazines [24,26]. This kind of metabolic liberation of phenylpiperazine has already been described for OX and for DRO [23,24]. Possible difficulties might occur if these compounds are formed as metabolites common with MeOPP. DRO has been shown to be metabolized in man to 4-HO-PP, the major metabolite of MeOPP, and to a minor extent to 4-hydroxyaniline, which may lead to misinterpretation of the analytical result [23]. Therefore, it is crucial to develop procedures which allow to differentiate an intake of the designer drug MeOPP from an intake of these therapeutic drugs. Fig. 4 shows the part of the metabolic pathways of MeOPP, DRO and OX which were found to be relevant for detection and differentiation of these drugs in urine within the STA. As controlled human studies on the designer drug MeOPP were not possible, a rat model was used for the differentiation studies. Comparison of DRO metabolites found in human and rat

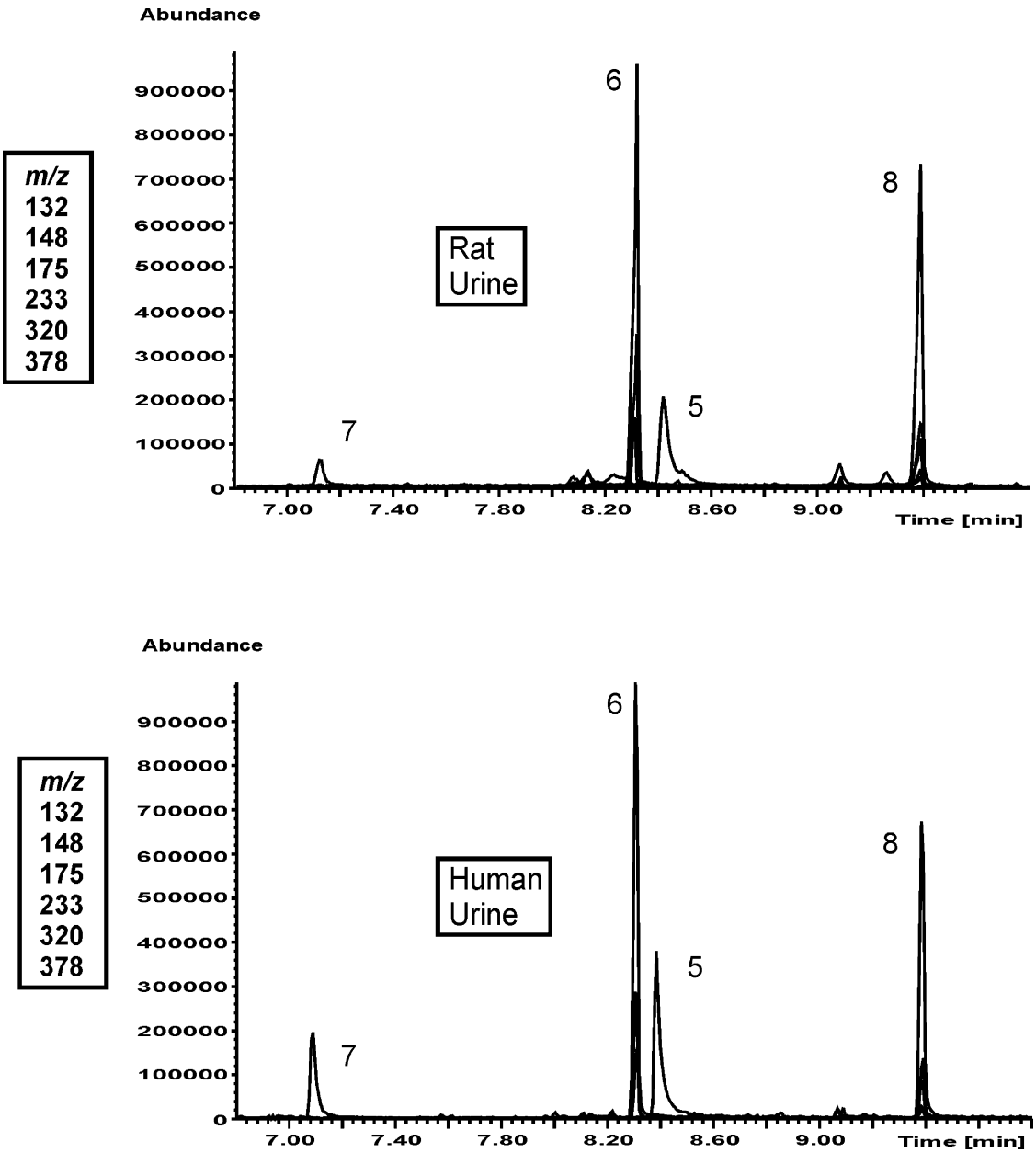

Fig. 5. Typical reconstructed mass chromatograms with the given ions of an acetylated extract of a rat urine sample collected over 24 h after application of a common therapeutic dose of 1.3 mg/kg BM of DRO (a) and of a human urine sample take 7.5 h after intake of the same dose of 1.3 mg/kg BM of DRO (b). They indicate the presence of DRO (peak no. 6) and its metabolites 4-HO-PP (peak no. 5), *N*-phenylpiperazine (peak no. 7), and hydroxy-DRO (peak no. 8).

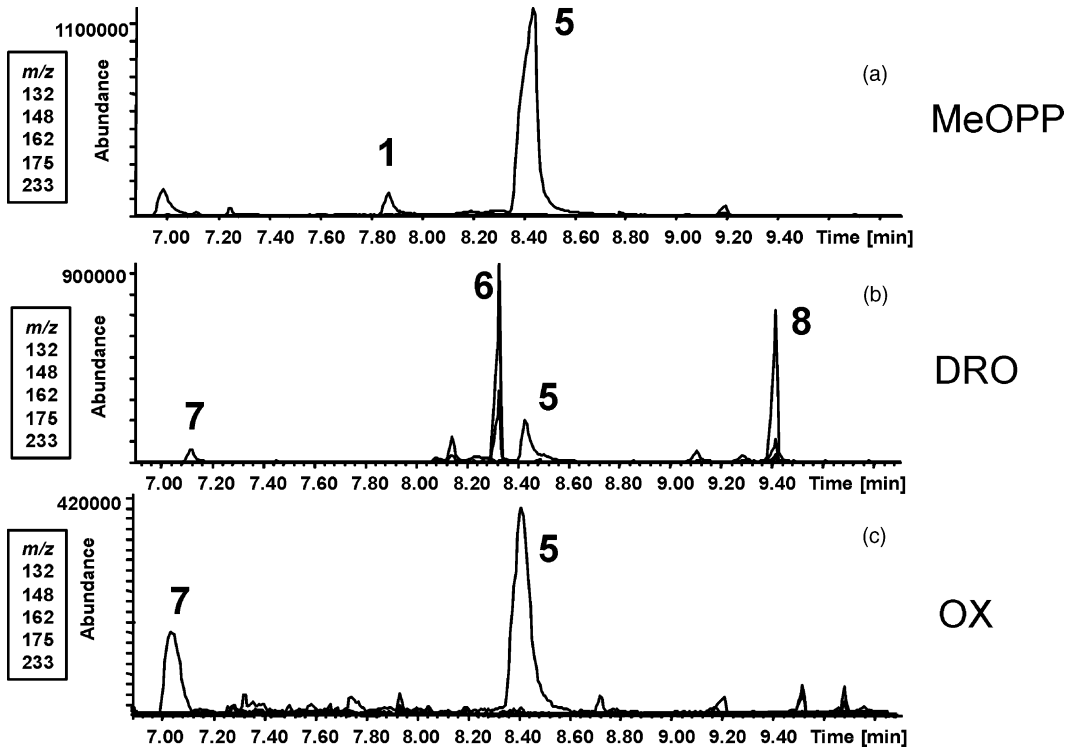

Fig. 6. Typical mass chromatograms with the given ions of acetylated extracts of rat urine collected over 24 h after administration of a common therapeutic dose of 1.0 mg/kg BM of MeOPP (a), 1.3 mg/kg BM of DRO (b) and of an urine after administration of a common therapeutic dose of 1.5 mg/kg BM of OX (c).

urine, proved that this model was suitable for such studies (Fig. 5).

Fig. 6 shows typical mass chromatograms with the given ions of acetylated extracts of rat urine samples collected over 24 h after administration of a dose of 1.0 mg/kg BM of MeOPP (a), of a common therapeutic dose of 1.3 mg/kg BM of DRO (b) and of a common therapeutic dose of 1.5 mg/kg BM of OX (c). The ion *m/z* 132 was used for indication of *N*-phenylpiperazine, *m/z* 148 for 4-HO-PP, *m/z* 162 for MeOPP, *m/z* 175 for DRO and 233 for HO–DRO. The peak numbers correspond to those used in Fig. 1. Using the described STA, an intake of MeOPP could be differentiated from an intake of DRO via the parent compounds MeOPP (peak no. 1) or DRO (peak no. 6) or via hydroxy-DRO (peak no. 8). 4-HO-PP (peak no. 5) is only a minor metabolite of DRO. After application of a common therapeutic dose of OX, the major metabolite detectable in urine was 4-HO-PP (peak no. 5) and to a minor extent *N*-phenylpiperazine (peak

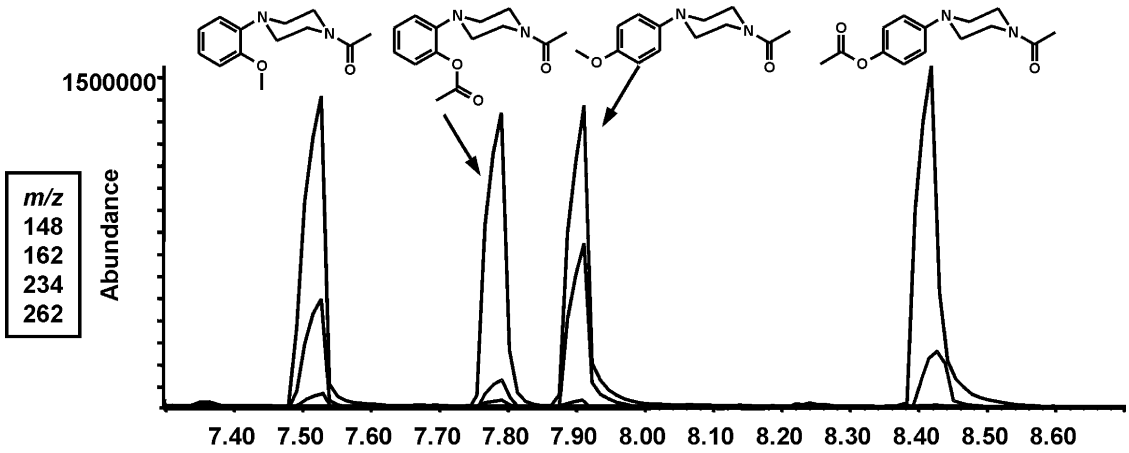

Fig. 7. Typical mass chromatograms with the given ions of a blank urine extract spiked with a mixture of MeOPP, 4-HO-PP and its isomers 2-MeOPP and 2-HO-PP (final concentration 100 ng/ml each) and acetylated.

no. 7). The parent compound OX could not be detected. In order to differentiate an intake of MeOPP from an intake of OX, the toxicologist should screen for the parent compound MeOPP (peak no. 1) as this compound is not formed from OX and for *N*-phenylpiperazine (peak no. 8), as this compound is not a metabolite of MeOPP.

There are also a wide variety of substituted 2-methoxy-phenylpiperazines, such as the antihypertensive drug urapidil or the antipsychotic drug fluanisone [24,26], some of which are also reported to be metabolized to the corresponding methoxy or hydroxy substituted phenylpiperazine isomers [24,43]. Just recently, this 2-methoxy substituted phenylpiperazine derivative has also been found on the illicit drug of abuse market [45–48]. As shown in Figs. 1 and 7, the corresponding isomers of the methoxy-phenylpiperazines and their *O*-demethylated metabolites could preferably be differentiated by their retention time, because their mass spectra are rather similar. Finally, it should be mentioned that the acetylated MeOPP metabolite 4-hydroxyaniline is identical with acetylated paracetamol, which may lead to misinterpretation.

4. Conclusions

The studies presented here showed that the authors' STA procedure allowed the detection of an intake of a dose of MeOPP that corresponds to a common drug users' dose in rat urine via the parent compound and its metabolite 4-HO-PP as target analytes. Only the detection of the parent compound allowed unequivocal proof of a MeOPP use, because the metabolites are not unique metabolites of MeOPP but also of the therapeutic drugs DRO and OX. A differentiation from an intake of DRO was also possible via DRO and its metabolite hydroxy-DRO. An intake of OX could be differentiated via *N*-phenylpiperazine, as this compound is not a metabolite of MeOPP. The corresponding isomers of MeOPP and its major metabolite 4-HO-PP, 2-MeOPP and 2-HO-PP which are metabolically formed from some therapeutic drugs such as urapidil or fluanisone, can be differentiated via their different gas chromatographic properties.

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