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Studies on the metabolism and toxicological detection of the amphetamine-like anorectic fenproporex in human urine by gas chromatography–mass spectrometry and fluorescence polarization immunoassay ☆

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Abstract

Studies on the metabolism and the toxicological analysis of fenproporex (*R,S*-3-[(1-phenyl-2-propyl)-amino]-propionitrile, FP) using GC–MS and fluorescence polarization immunoassay are described. The metabolites were identified in urine samples of volunteers by GC–MS after cleavage of conjugates, extraction and acetylation. Besides unchanged FP, fourteen metabolites, including amphetamine, could be identified. Two partially overlapping metabolic pathways could be postulated: ring degradation by one- and two-fold aromatic hydroxylation followed by methylation and side chain degradation by N-dealkylation to amphetamine (AM). A minor pathway leads via β-hydroxylation of AM to norephedrine. For GC–MS detection, the systematic toxicological analysis procedure including acid hydrolysis, extraction at pH 8–9 and acetylation was suitable (detection limits 50 ng/ml for FP and 100 ng/ml for AM). Excretion studies showed, that only AM but neither FP nor its specific metabolites were detectable 30–60 h after ingestion of 20 mg of FP. Therefore, misinterpretation can occur. The Abbott TDx FPIA amphetamine/methamphetamine II gave positive results up to 58 h. All the positive immunoassay results could be confirmed by the described GC–MS procedure.

Keywords: Fenproporex

1. Introduction

Fenproporex (*R,S*-3-[(1-phenyl-2-propyl)-amino]-propionitrile) is a widely used anorectic. Many authors claimed that fenproporex lacked habit-forming and central stimulant properties, although it is an amphetamine derivative [2,3]. It was postulated that the presence of the cyano group prevents FP from N-dealkylation. However, other authors reported metabolic N-dealkylation of FP to amphetamine (AM) [4–6]. AM was found in urine or hair samples after ingestion of FP in some analytical studies on anorectics by immunoassay, HPLC, GC or GC–MS [7–9]. Amphetamine and fenproporex levels in urine

☆Dedicated to Professor Dr. Manfred R. Moeller, Homburg (Saar), on the occasion of his 60th birthday. Part of these results was reported at the 34th International TIAFT Meeting, Interlaken (Switzerland), 1996 [1].

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after single-dose [10] and multidose administration of FP were published [11]. Unfortunately, only the parent compound and amphetamine are monitored in most publications. Possible metabolites, which could possibly help in differentiation, were not considered. In a previous study, we showed that hydroxy metabolites of mefenorex, a similar anorectic, were excreted for a much longer time than the parent compound, thus allowing a longer time of differentiation [12]. Therefore, we have reinvestigated the metabolism of FP in humans using GC–MS and we have studied the toxicological detection of FP and its metabolites in human urine by fluorescence polarization immunoassays (FPIA) and within our systematic toxicological analysis (STA) procedure by GC–MS. The aim of our studies was to investigate which metabolites are detectable in urine and for how long they are detected and whether the intake of FP can be differentiated from an intake of AM by detection of FP specific (non-N-dealkylated) metabolites.

2. Experimental

2.1. Chemicals and reagents

All chemicals used were obtained from Merck (Darmstadt, Germany) and were of analytical grade. Fenproporex tablets each containing 10 mg of FP were obtained from a French pharmacy.

2.2. Urine samples

After informing them according to the declaration of Helsinki and obtaining written consent, three healthy volunteers received a single oral dose of 20 mg of FP. Urine samples were collected every 4 h for 6 days. All samples were directly analyzed and then stored at −20°C before further analysis. Blank urine samples were collected before drug administration to check whether the samples were free from interfering compounds.

2.3. Sample preparation for metabolism studies

A 5-ml portion of urine was adjusted to pH 5.2 with acetic acid and incubated at 38°C for 12 h with 100 μl of a mixture of glucuronidase and arylsulfatase (100 000 Fishman units per ml), then adjusted to pH 8–9. In order to get equal conditions as after acid hydrolysis (see Section 2.4) the sample was mixed with a mixture of 1.5 ml of 37% hydrochloric acid, 2.5 ml of 2.3 mol/l aqueous ammonium sulphate and 2 ml of a 10 mol/l aqueous sodium hydroxide solution. The sample was cooled on ice and 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 transfered and evaporated to dryness, and the residue was acetylated with 50 μl of an acetic anhydride–pyridine mixture (3:2, v/v) for 10 min under microwave irradiation [13,14]. After evaporation, the residue was dissolved in 50 μl of methanol and 2 μl of this solution were injected into the gas chromatograph. The same procedure with the exception of enzymatic hydrolysis was used to study whether unconjugated metabolites of FP are excreted.

2.4. Sample preparation for toxicological analysis

A 5-ml portion of urine was refluxed with 1.5 ml of 37% hydrochloric acid for 15 min. Following hydrolysis, the sample was basified with 2 ml of 10 mol/l aqueous sodium hydroxide and the resulting solution was mixed with 2.5 ml of 2.3 mol/l aqueous ammonium sulphate to obtain a pH between 8 and 9. 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 transfered and evaporated to dryness. The residue was derivatized by acetylation with 50 μl of an acetic anhydride–pyridine mixture (3:2, v/v) for 5 min under microwave irradiation [13,14]. After evaporation of the derivatization mixture, the residue was dissolved in 50 μl of methanol and 2 μl were injected into the gas chromatograph.

2.5. Gas chromatography–mass spectrometry

FP and its metabolites were separated and identified in acetylated urine extracts using a Hewlett-Packard (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 capillary (12 m×0.2 mm I.D.), cross linked methylsilicone, 330 nm film thickness; injection port temperature, 280°C; carrier gas, helium; flow-rate 1 ml/min; column temperature, programmed from 100 to 310°C at 30°/min, initial time 3 min, final time 8 min. The MS conditions were as follows: full scan mode; EI ionization mode: ionization energy, 70 eV; ion source temperature, 220°C; capillary direct interface heated at 260°C.

For toxicological detection of FP and its metabolites, mass chromatography with the selected ions *m/z* 97, 139, 176, 234, 86, 118, 134 and 164 was used. Generation of the mass chromatograms could be started by clicking the corresponding pull down menu which executes the user defined macros [15] (the macros can be obtained from the authors: e-mail: Hans.Maurer@med-rz.uni-sb.de). The identity of the peaks in the mass chromatograms was confirmed by computerized comparison [16] of the peaks underlying mass spectra with reference spectra (Fig. 1) recorded during this study.

2.6. Fluorescence polarization immunoassays (FPIA)

Native urine samples from the volunteers were used for immunological determination. The TDx system of Abbott (Irving, TX, USA) with the amphetamine/methamphetamine II assay (AM/MA II) was applied. The cut-off value and the detection limit recommended by the manufacturers were 300 and 100 ng/ml, respectively. To determine the cross reactivities of FP with this assay, blank urine samples were spiked with FP in concentrations of 100–1 000 000 ng/ml.

3. Results and discussion

3.1. Sample preparation

Cleavage of conjugates by enzymatic or acid hydrolysis was necessary before extraction since the expected hydroxy metabolites of FP were excreted mostly as conjugates. For studies on the metabolism, gentle enzymatic hydrolysis was preferred. For studies on the toxicological detection rapid acid hydrolysis was performed. The samples were extracted at pH 8–9. The (metabolic) introduction of an aromatic hydroxy group into a phenethylamine derivative leads to phenol bases which are best extracted at pH 8–9. Using a more alkaline pH for extraction of AM derivatives leads to the loss of such hydroxy metabolites which are often the metabolites which are excreted for a longer time than the parent compounds [12,17–21]. The high volatility of the amphetamines required very careful sample preparation, especially gentle evaporation of the extraction and derivatization mixtures, for reproducible results. Derivatization of the extracts was required for sensitive detection.

The analytical recovery of FP and its metabolite AM, determined after enzymatic hydrolysis at concentration levels of 500 and 1000 ng/ml, respectively, was 82±4% for FP and 80±5% for AM. The analytical recovery of FP and its metabolite AM determined after acid hydrolysis at concentration levels of 500 and 1000 ng/ml, respectively, was 89±4% for FP and 88±5% for AM. It has to be noted that under routine laboratory conditions the recoveries were lower (70–80% for FP and 50–70% for AM), mainly resulting from evaporation losses.

3.2. Identification of metabolites

The urinary metabolites of FP were identified by EI-MS after enzymatic hydrolysis, extraction, acetylation and GC separation. The EI mass spectra of the postulated metabolites were interpreted in correlation to that of the parent compound according to the rules described by McLafferty and Turecek [22]. The mass spectra, the structures and the predominant EI fragmentation patterns of FP and its metabolites after acetylation are shown in Fig. 1 (The gas chromatographic retention indices (RI) are also given for GC detection as described below.). Besides the unchanged parent compound FP (**I**), the following fourteen metabolites could be identified: the two isomers of hydroxy-FP (**II**, **III**), dihydroxy-FP (**IV**), hydroxy-methoxy-FP (**V**), N-desalkyl-FP (amphetamine, **VI**), two isomers of N-desalkyl-hydroxy-FP (**VII**, **VIII**), N-desalkyl-dihydroxy-FP (**IX**), N-desalkylhydroxymethoxy-FP (**X**), N-desalkylhydroxyalkyl-FP (norephedrine, **XI**), desaminooxo-FP (**XII**), desaminooxohydroxy-FP (**XIII**), desaminooxodihydroxy-FP (**XIV**) and de-

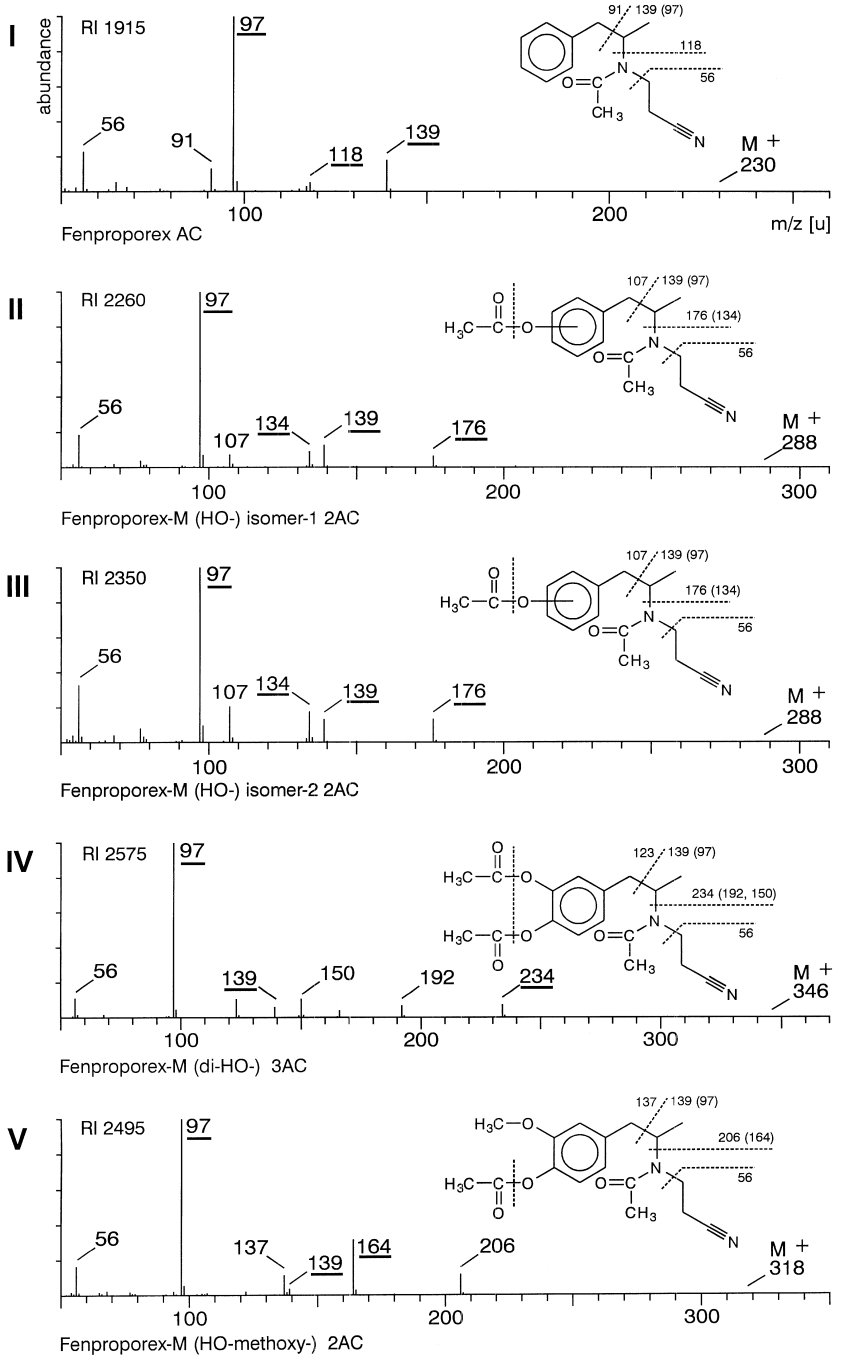

Fig. 1. Mass spectra, predominant fragmentation patterns, structures and gas chromatographic retention indices (RI) of FP and its metabolites after acetylation for precise identification. The numbers of the spectra correspond to those in Fig. 2. Ions selected for the toxicological detection are underlined. (The axes are only labelled for I.).

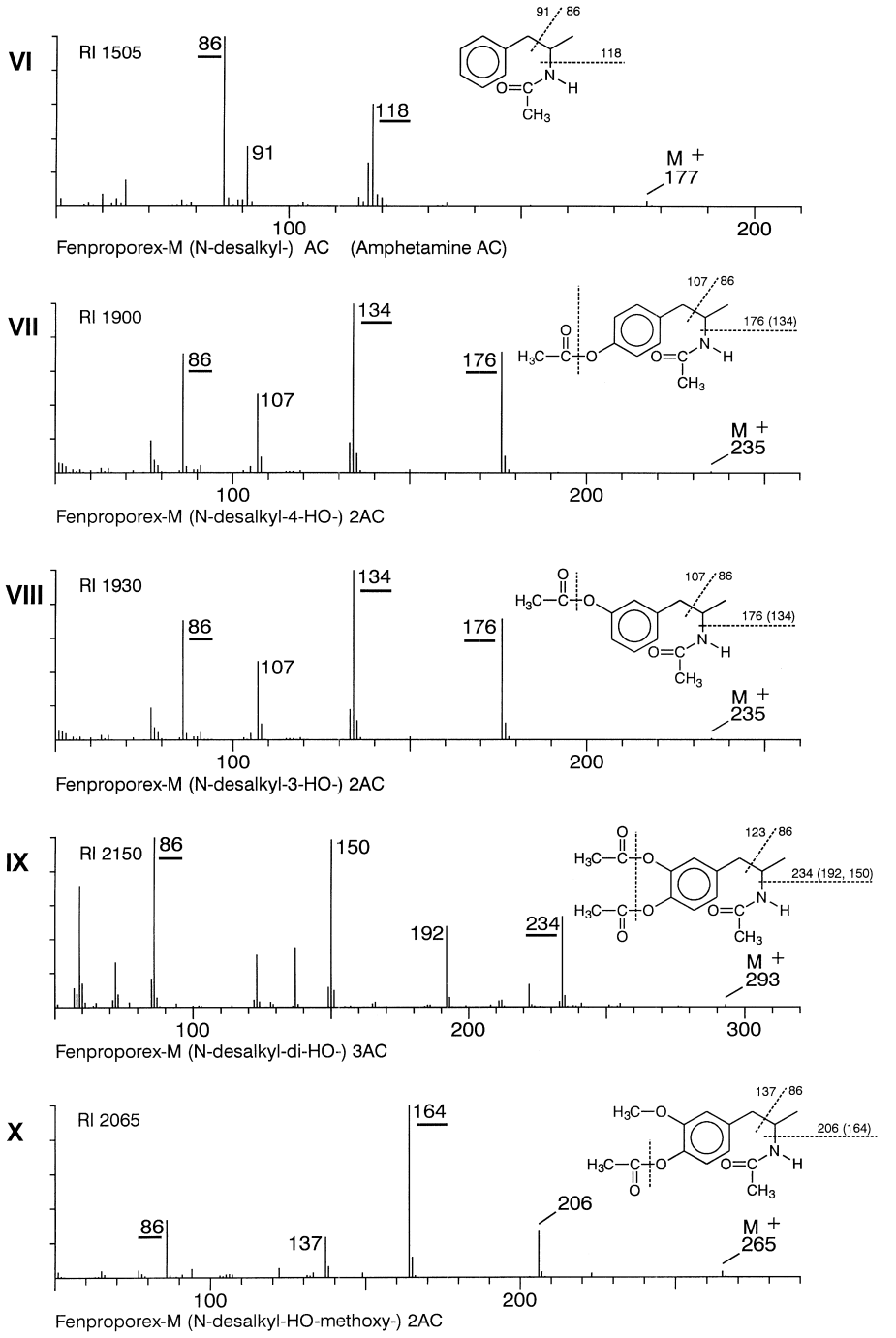

Fig. 1. (*continued*)

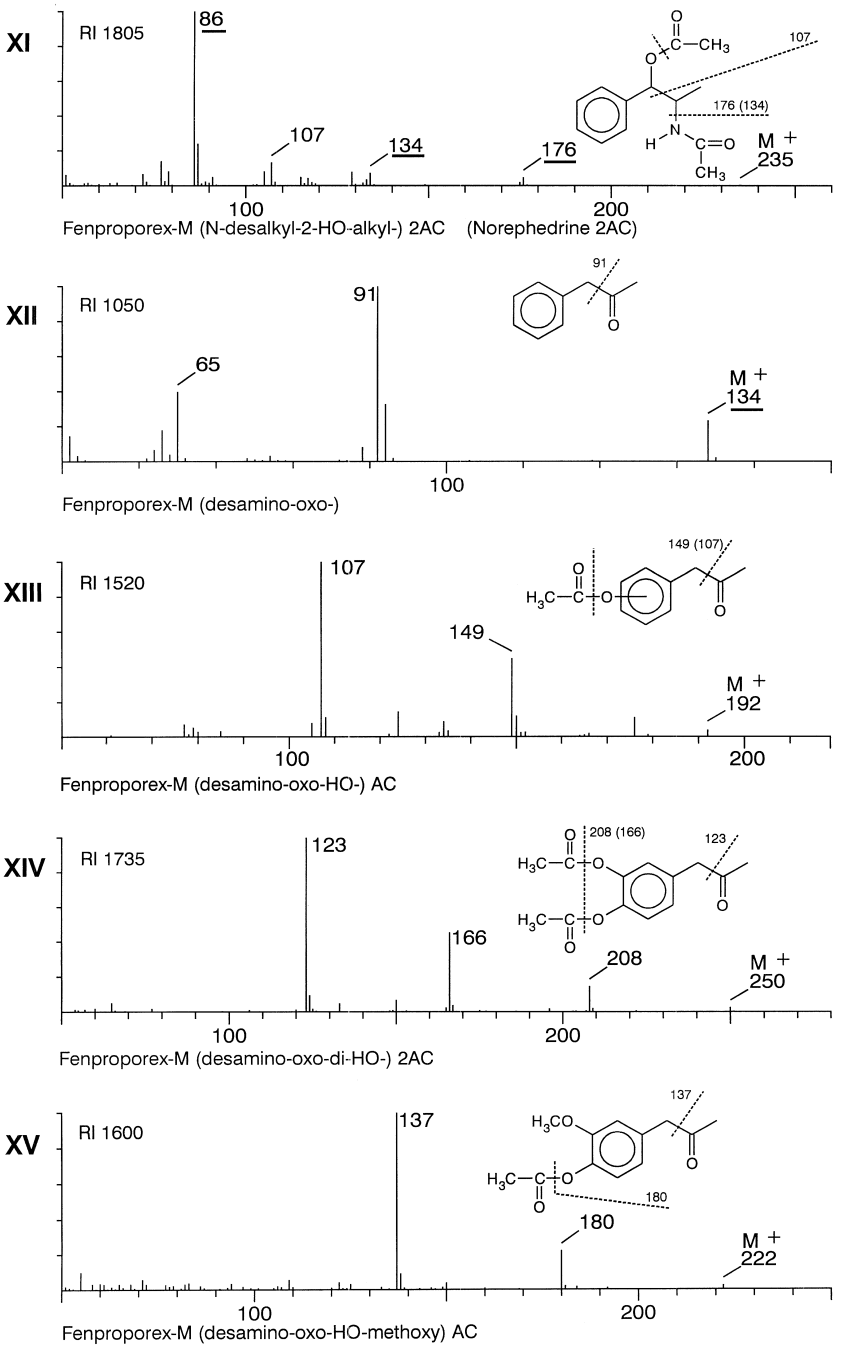

Fig. 1. (*continued*)

saminooxohydroxymethoxy-FP (**XV**). The hydroxy metabolites (**II–V, VII–X** and **XIII–XV**) were partly excreted as conjugates cleavable by glucuronidase or arylsulfatase. Most of the metabolites are described here for the first time. This is due to the fact that the preceeding studies focused on the N-dealkylation

step to AM. Only in the studies of Coutts et al. two other metabolites were described, HO-AM and HO-FP [5]. On the basis of the identified metabolites the following metabolic pathways, depicted in Fig. 2, could be postulated: single- and double aromatic hydroxylation and methylation to hydroxymethoxy-FP and N-desalkylation to amphetamine which leads via oxidative N-desamination to desaminooxo-fenproporex. A minor pathway, β-hydroxylation of the amphetamine results in the formation of norephedrine. FP and its metabolites **II**–**XII** could be detected in urine from the volunteers. The metabolites **XI**–**XV** were detected only in urine from patients with known heavy abuse of FP.

3.3. Detection by GC–MS within the STA

The full mass spectra recorded during temperature-programmed GC were evaluated using mass chromatography. Generation of the mass chromatograms could be started by clicking the corresponding pull down menu which executes the user defined macros. Fig. 3 shows the reconstructed mass chromatograms indicating the presence of FP and its metabolites in an acetylated extract of a urine sample from a volunteer 4 h after ingestion of 20 mg of FP. The selected ions m/z 97 and 139 were used for identification of the metabolites of FP with an unchanged side chain. The selected ion m/z 86 was used for indicating the presence of N-dealkylated metabolites of FP. The selected ion m/z 118 was used for indicating the presence of FP metabolites with an unchanged ring structure. The selected ions m/z 134, 176 and 234 were used for indicating the presence of hydroxy or dihydroxy metabolites of FP. Hydroxy-methoxy metabolites were indicated by the selected ion m/z 164. Screening for the deamino-oxo metabolites was not useful, since they could only be detected after massive abuse of FP. As shown in Fig. 4, the identity of peaks in the mass chromatograms was confirmed by computerized comparison of the underlying mass spectrum with reference spectra (Fig. 1) recorded during this study. In our experience, the gas chromatographic RIs provide preliminary indications and may be useful to gas chromatographers without a GC–MS facility. There-

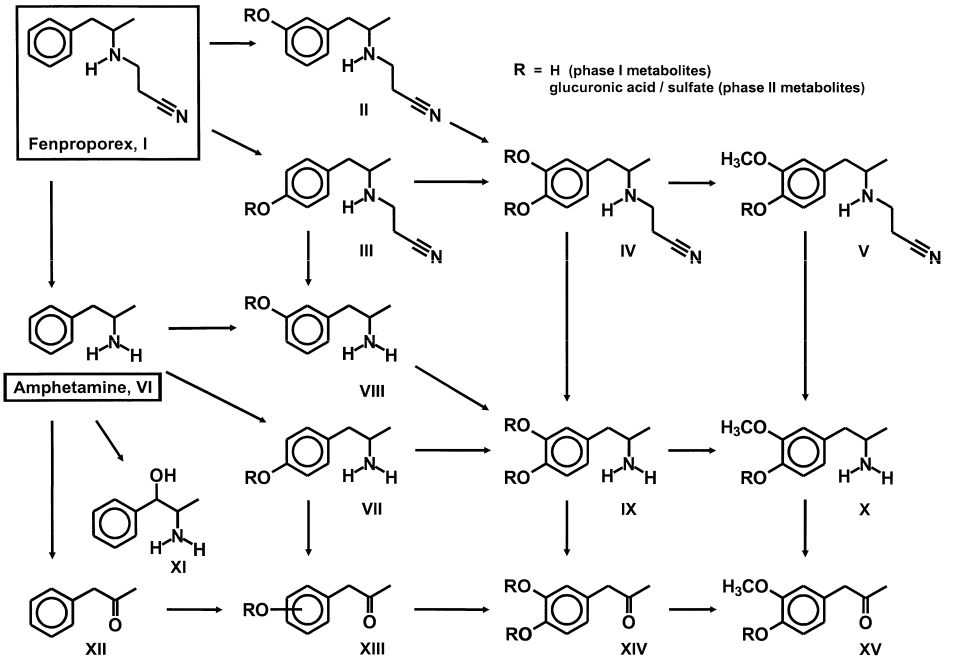

Fig. 2. Proposed scheme for the metabolism of FP in humans. The metabolites **II**–**V**, **VII**–**X** and **XIII**–**XV** were also present as glucuronic and/or sulfuric acid conjugates in urine, indicated by the substituent R.

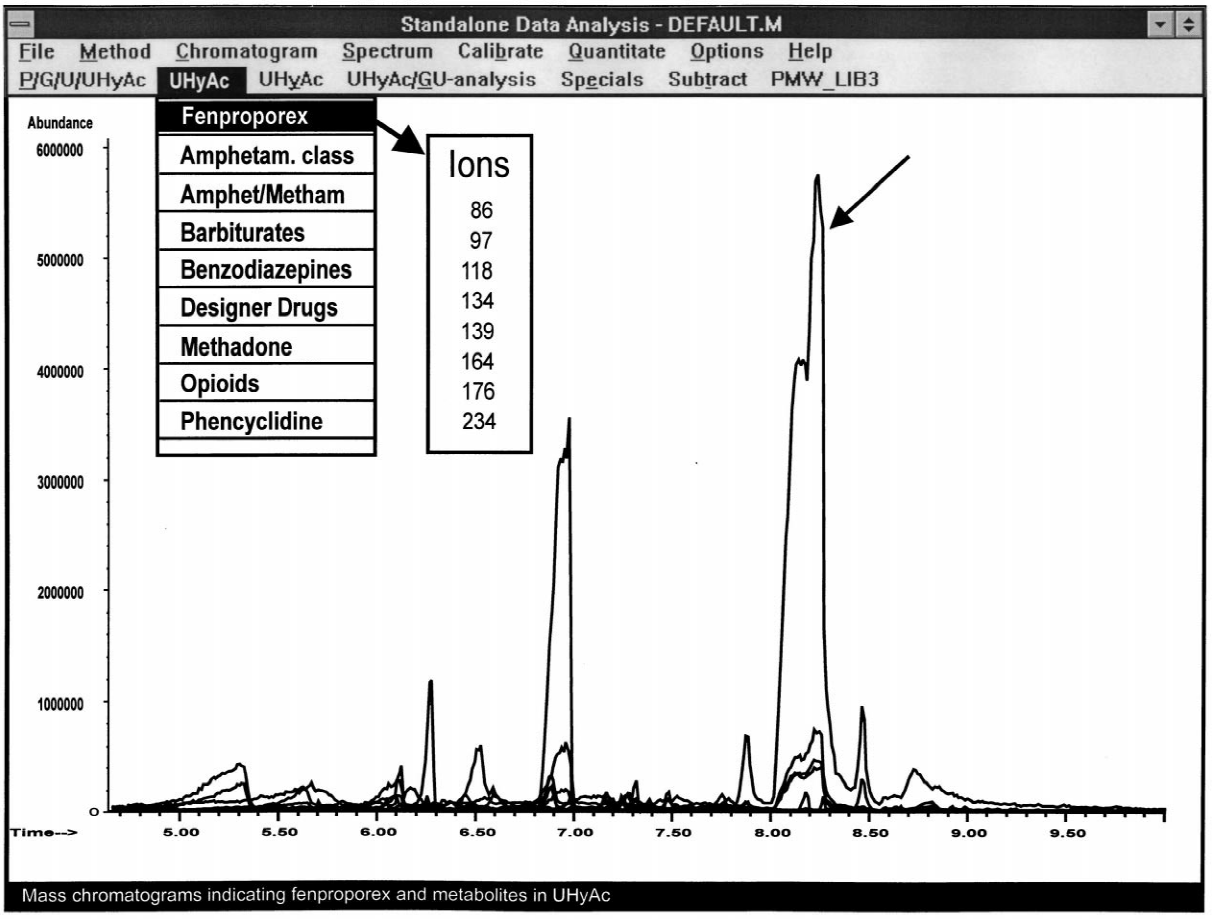

Fig. 3. Typical mass chromatograms with the ions m/z 97, 139, 176, 234, 86, 118, 134 and 164. They indicate the presence of FP and its metabolites in an acetylated extract of a urine sample taken 4 h after ingestion of 20 mg of FP. The merged chromatograms can be differentiated by their colors on a color screen.

fore, they are also given in Fig. 1. The RIs were recorded during the GC–MS procedure (Section 2.5) and calculated in correlation with the Kovats' indices [23] of the components of a standard solution of typical drugs which is measured daily for testing the GC–MS performance [24,25]. The reproducibility of retention indices measured on capillary columns was better using a mixture of drugs than that of the homologous hydrocarbons recommended by Kovats. Because of the mass spectral identification, interferences by biomolecules or further drugs could be excluded. It should be noted that AM and its metabolites can also be metabolically formed from other derivatives [21] like amphetaminil, ethylamphetamine [26], fenetylline, methamphetamine [16,27], clobenzorex [28], mefenorex [12], famprofazone [29–31] or selegiline [17]. However, in urine samples, in which specific metabolites are excreted along with AM, the use of these drugs can be differentiated from AM abuse. The GC and MS data of these are included in our handbook and library [16,27] together with the data of all the endogenous biomolecules detectable after the described procedure. The limit of detection of FP in urine was 50 ng/ml and that of the metabolite AM 100 ng/ml ($S/N=3$) under routine MS conditions.

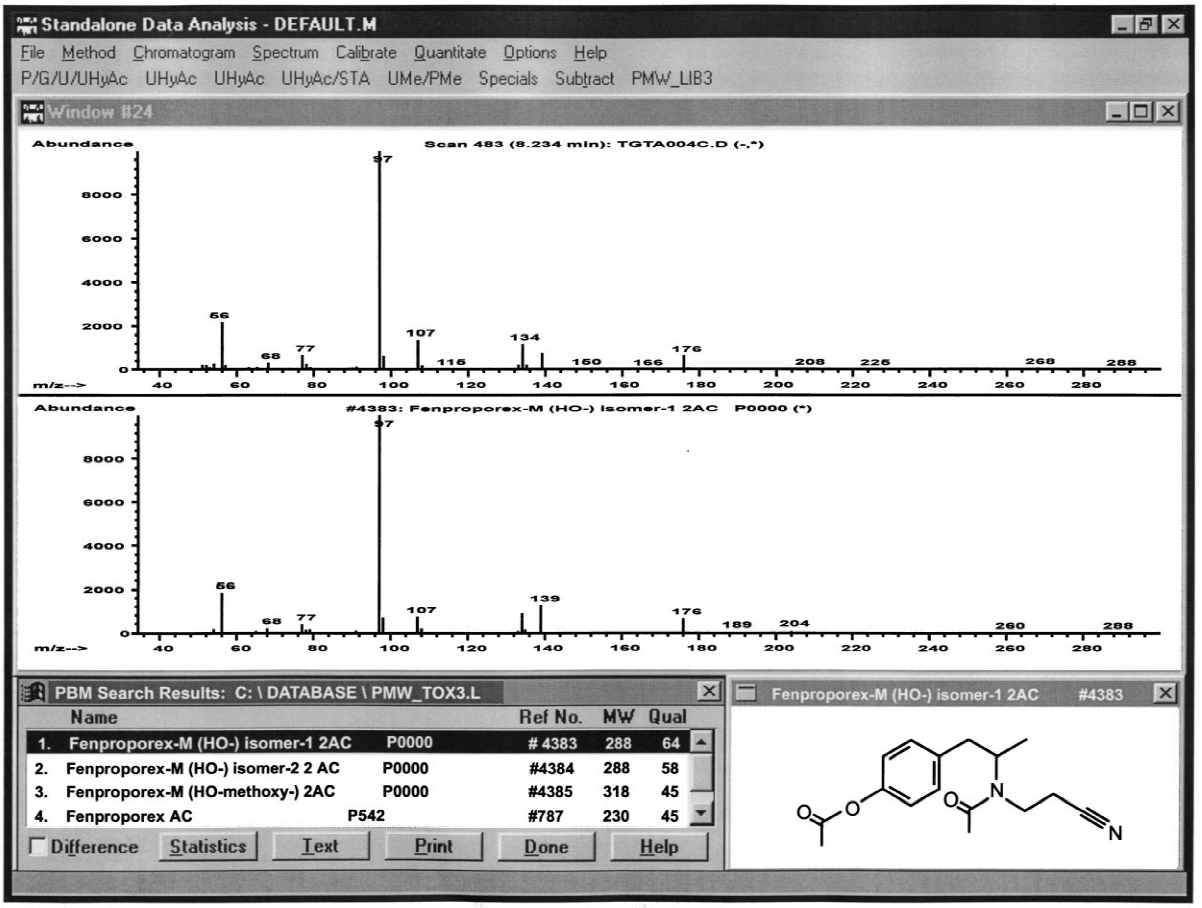

Fig. 4. Mass spectrum underlying the marked peak in Fig. 3, the reference spectrum, the structure, and the hit list found by computer library search.

3.4. Detection by FPIA

The cross-reactivity values of FP with the AM/MA II assay ranged between 1.4 and 2.3%. The TDx values measured during our excretion study ranged between 100 and 10 000 ng/ml. These data are in accordance with that of De la Torre et al. [7]. Since FP shows only minor cross-reactivity with the AM/MA II assay, its dealkylated metabolites should be responsible for the positive results. As described in Section 3.5, AM is the metabolite which is excreted for the longest time. Therefore, at least in the late phase of excretion the TDx results should correspond to the presence of AM.

3.5. Duration of detectability of FP and its metabolites in urine by GC–MS and FPIA

The duration of detectability of FP and its metabolites in urine by GC–MS and FPIA is shown in Fig. 5. After a single oral dose of 20 mg of FP the AM/MA II assay gave positive results in urine up to 56 h taking into consideration the cut-off value recommended by the manufacturer (300 ng/ml). Using GC–MS, the parent compound FP could be detected for only 12–16 h. Its specific (non-dealkylated) metabolites could be detected for a longer time (up to 28 h). The metabolite AM could be detected for up to 60 h. All the positive immuno-

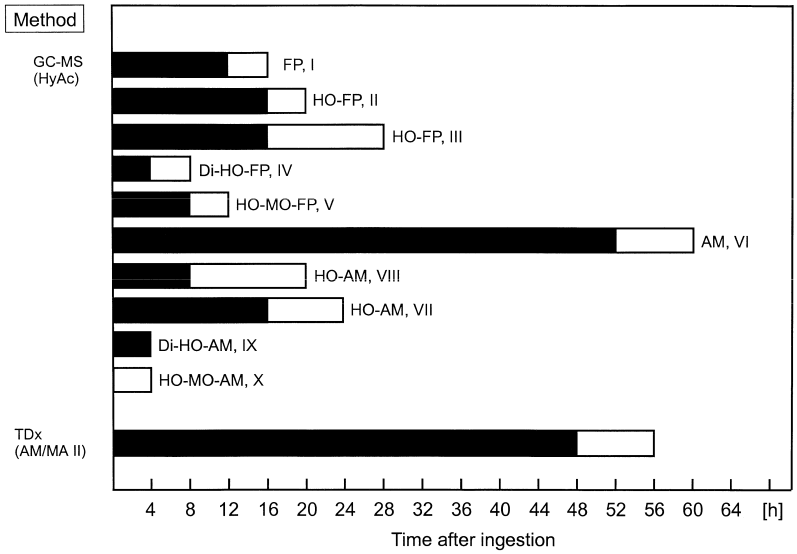

Fig. 5. Duration of detectability of FP and its main metabolites by GC–MS and by the TDx assay AM/MA II (cut-off 300 ng/ml) in urine samples after ingestion of 20 mg of FP (n=3). The black portion of the bar indicates the shortest and the white represents the longest detection times found for the three volunteers.

assay results (>cut-off) could be confirmed by the described GC–MS procedure. The variation of the time of excretion of FP and its metabolites may be caused by inter-individual differences e.g. relative body mass and/or renal function. Since only amphetamine could be detected from 30 to 60 h after ingestion, a therapeutic intake of FP could not be differentiated from an amphetamine abuse during this period. Therefore, misinterpretation of immunoassay and GC–MS results is possible. It should be noted that the detection of hydroxy-FP can increase the time of differentiation up to 28 h after ingestion, whereas the parent compound could be detected only up to 16 h. Therefore, the hydroxy metabolites of FP should also be screened in case of GC–MS confirmation of positive TDx results e.g. in post-mortem, driving under the influence and sports testing laboratories (see also Section 3.6).

3.6. Forensic implications

As noted in previous publications [12,21,28] confirmation of positive IA results for amphetamines should not be limited to detection of AM and MA by GC–MS in the single-ion monitoring (SIM) mode. AM- and MA-derived medicaments must be considered as part of a proper interpretation of amphetamine positive results. The full-scan mode is to be preferred for this purpose. Since the hydroxy metabolites of such medicaments are excreted for a much longer time, screening for the parent compounds in addition to MA or AM may not be sufficient at least if low cut-off values (300 ng/ml) are chosen. Cody et al. [11] determined AM and FP levels after administration of FP. In their study, the parent compound was detectable in every urine sample with AM results greater than 500 ng/ml (cut-off in their study). However, if lower cut-offs are chosen, e.g. in forensic or clinical toxicology or in doping control, detection of the parent compound is not sufficient, a conclusion which can be drawn from the same study of Cody. FP levels were quite low in this study. Even in cases of relatively high amphetamine levels (up to 1279 ng/ml), FP levels reached values only between the LOD and the LOQ of the GC–MS method (2–5 ng/ml). In addition, amphetamine results of up to 477 ng/ml could not be confirmed by detection of FP. Detection of the hydroxy metabolites may help

extend the time of differentiation of illicit amphetamine abuse from intake of medicaments. However, in the late phase of excretion after intake of amphetamine-derived medicaments, AM or MA are often the only metabolites which can be detected in urine. In such urine samples, differentiation of illicit AM or MA intake from the intake of such medicaments may not be possible. To say it clearly and unambiguously, a positive amphetamine immunoassay result, even if confirmed as AM or MA by GC–MS in the SIM mode, can be caused by intake of legal medication. Determination of the enantiomeric composition of AM or MA may help in some cases e.g. if pure *S*-(+)-enantiomers of AM or MA were ingested. The presence of only this enantiomer of AM in urine would be inconsistent with use of racemic AM-derived medicaments.

4. Conclusions

Our reinvestigation on the metabolism of FP showed that FP is metabolized via two partly overlapping pathways to fourteen metabolites. The GC–MS procedure described here allowed the identification of the urinary metabolites of FP and precise and sensitive detection of FP and/or its metabolites in urine for up to 60 h after ingestion of a 20-mg dose. Other AM derivatives [12,17,18,20,28,32] as well as most of the toxicologically relevant drugs like barbiturates, benzodiazepines, opioids, analgesics, antidepressants, neuroleptics, antiparkinsonians, anticonvulsants, antihistamines, β-blockers, antiarrhythmics, and laxatives could also be detected and differentiated within the same procedure by clicking the corresponding pull down menu (e.g. ‘amphetamine class’) executing user defined macros followed by library search of the spectra underlying the peaks [15,33,34].

The AM/MA II assay showed positive results in urine up to 56 h after ingestion of FP. All the positive results (>cut-off) could be confirmed by the described GC–MS procedure. Misinterpretation of the origin of positive immunoassay and even of GC–MS results is possible, since the parent compound FP or its specific metabolites are not detectable for as long as the metabolite AM.

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