Metabolic Precursors to Amphetamine and Methamphetamine

J. T. Cody
Clinical Investigations
Wilford Hall Medical Center
Lackland AFB, TX 78236-5319
United States of America

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ABSTRACT: Analysis and interpretation of amphetamine results is a challenging process made difficult by a number of factors. One of the complications comes from determination of the origin of amphetamine or methamphetamine in a sample. Given the relatively rare occasions that either of these two drugs are prescribed, legal prescription of one of these drugs is seldom a reason for positive findings. A number of other precursor compounds are metabolized by the body to amphetamine or methamphetamine, many of which could be used for legitimate reasons. Fourteen different metabolic precursors of amphetamine or methamphetamine are included in this review. They are amphetaminil, benzphetamine, clobenzorex, deprenyl, dimethylamphetamine, ethylamphetamine, famprofazone, fencamine, fenethylline, fenproporex, furfenorex, mefenorex, mesocarb, and prenylamine. Medical use, metabolism, analysis, and interpretation are described to afford sufficient information to evaluate the possible involvement of these drugs in positive amphetamine or methamphetamine results.

KEY WORDS: Amphetamine, amphetaminil, benzphetamine, clobenzorex, deprenyl, dimethylamphetamine, ethylamphetamine, famprofazone, fencamine, fenethylline, fenproporex, furfenorex, mefenorex, mesocarb, metabolic precursor, methamphetamine, prenylamine.

INTRODUCTION

Amphetamines have a long history of abuse and are challenging both in their analysis and interpretation. Amphetamine and methamphetamine comprise the majority of abuse of this drug class seen throughout the world. In addition to the analytical challenges, interpretation of amphetamine positive results is often a complicated problem. Excretion of amphetamines is dramatically influenced by the urinary pH, thus making an evaluation of the measured concentrations difficult. In addition, the enantiomeric composition of methamphetamine and amphetamine in the sample is critical information due to the availability of *l*-methamphetamine in the over-the-counter Vicks Inhaler.

When the presence of amphetamine or methamphetamine is reported, concern for the illicit use of the drugs immediately surfaces. However, interpretation of results must always include the potential for the use to have been legitimate, which most often translates to use pursuant to medical prescription. Amphetamine- and methamphetamine-containing drugs are prescribed, although not widely, because of their high potential for abuse and rapid development of tolerance.

While issues like the Vicks Inhaler complicate the interpretation of results, its role and interpretation is well known and understood. An even more complicating, and less well known, factor in the interpretation of positive results is that a number of precursor compounds are metabolized in vivo to methamphetamine or amphetamine. For purposes of this review, the term *precursor* compound will be used to refer to a compound that is metabolized by the body to either amphetamine or methamphetamine. Several of these drugs, such as deprenyl and benzphetamine, have been reported as precursors to amphetamines and their role is generally known. There are a number of other drugs available, however, that are also converted to methamphetamine and/or amphetamine, but are less well known. Without this critical information, proper interpretation of analytical results could be problematical.

Drugs that have been shown to be metabolic precursors to amphetamine or methamphetamine include: amphetaminil [54,100], benzphetamine [10,21,23,57,59,79,90], clobenzorex [48], deprenyl [36,52,63,80,94,98,101,102], dimethylamphetamine [10,17,58,113,122], ethylamphetamine [5–10,33,75,120], famprofazone [85,88,91], fencamine [76], fenethylline [35,50,56,71,89], fenproporex [9,11,87,115], furfenorex [10,20,60,79], mefenorex [16,37,87,120], mesocarb [96,109], and prenylamine [34,45–47,92,93,99]. Although many of these drugs are not universally available throughout the world, one or more of these drugs are available in essentially every part of the world.

[a] The views expressed in this article are those of the author and do not reflect the official policy of the U.S. Department of Defense or other departments of the U.S. Government.

Since these drugs are available in many different countries throughout the world, they are often referred to by several different names. The names for these drugs used in this review are the most common names associated with these compounds. One possible exception is deprenyl, which is also often called selegiline. A compilation of the chemical name, Chemical Abstract Service (CAS) number, and common names for these drugs can be found in Tables 1. The chemical structures of these compounds are shown in Section II-B where their metabolic and analytical procedures are discussed.

These 14 different compounds are metabolized by the body to amphetamine or methamphetamine. When available, information is also presented concerning the percentage of the dose converted to amphetamine or methamphetamine, enantiomeric distribution, and the potential for analysis of the parent or other unique metabolite that would allow easy differentiation of the use of one of these drugs from the direct use of amphetamine or methamphetamine.

I. MEDICAL USES

A. Amphetamine and Methamphetamine

Amphetamine and methamphetamine are currently available by prescription, but are listed as schedule II controlled substances (drugs with legitimate medical indications but high potential for abuse). Current indications for use of amphetamine are narcolepsy, attention deficit disorder in children, and short-term weight loss. Indications for the prescription of methamphetamine include treatment of attention deficit disorder in children and exogenous obesity [95].

B. Precursor Compounds

Precursor compounds are responsible for the production of amphetamine or methamphetamine (or both) in the bodies of the individuals who have taken the drug. In this regard, these compounds function as *prodrugs* in that they are transformed by the body into another biologically-active compound. It is appropriate to think of these compounds as prodrugs except, in the more classic sense, the term prodrug is used to indicate a compound that, although administered, is not the actual drug desired in the treatment regimen, but must be transformed by normal metabolic processes to the drug of interest. In fact, the compound administered may not by itself have any, or at least not the desired, biological activity.

Prodrugs are typically used in cases where, for some reason, the desired drug cannot be administered to the individual and therefore another compound is. The actual desired drug is then produced by normal metabolic pathways once in the body. An example of this is the administration of *l*-dopa as treatment for a deficiency of dopamine in the brain. Dopamine cannot be administered directly because it does not cross the blood brain barrier. *l*-Dopa does cross the barrier and is a metabolic precursor for dopamine. Therefore the net result of administration of *l*-dopa is increased production of dopamine in the brain.

Most of the drugs discussed in this section have their own activity and are not administered for the purpose of amphetamine or methamphetamine production, although several (including deprenyl and fenethylline) have had their activity attributed, at least in part, to amphetamine derived from the drugs rather than from the drugs themselves.

Many of these precursor compounds fall in the therapeutic category of anorexics with some degree of effectiveness in the treatment of obesity. Benzphetamine, ethylamphetamine, fenproporex, furfenorex, and mefenorex all belong to this therapeutic category. These compounds were often developed in an attempt to separate the desired anorexic effect from the typical central effects produced when using amphetamine or methamphetamine.

Amphetaminil is a psychotropic drug used for the treatment of fatigue, depression, and potency disorders, as well as narcolepsy [107]. It has also been used in an evaluation of the treatment of hyperkinetic children [81] and as an anorexic [51]. In combination with other medications, amphetaminil has also been used as a tonic and in the treatment of hypotension [103].

Benzphetamine is prescribed as an anorexic in the short-term treatment of obesity as an adjunct to a reduced calorie diet [95].

The drug *clobenzorex* is an anorexic, but additionally shows activity as a sympathomimetic amine [51]. Its primary use is as an anorexic in the short-term treatment of moderate to severe obesity [103,107].

Deprenyl is primarily used in the treatment of Parkinson's disease and is most often used in combination with *l*-dopa. Co-administration of deprenyl enhances the activity of *l*-dopa and decreases adverse side effects seen when *l*-dopa is administered alone [95]. At typical therapeutic levels, deprenyl functions as a potent monoamine oxidase inhibitor and is specific for the B form of the enzyme [52]. The activity of deprenyl has, at least in part, been attributed by some investigators to the effects of its amphetamine metabolite on the uptake of biogenic amines [63]. The fact that methamphetamine and amphetamine are produced from deprenyl is not a question in this case, nor are their functions. However, the role these two

Table 1. Chemical name, alternate common names, and chemical abstract number of compounds metabolized to amphetamine or methamphetamine

Name[a] and structure desig.		Chemical name; Other names [b]	CAS no. [c]
Amphetamine-producing compounds			
Amphetaminil	3	α-[(1-Methyl-2-phenylethyl)amino]benzeneacetonitrile; Amfetaminal, Amfetaminyl, AN-1, Aponeuron, Cyanobenzylamphetamine, Ton-O_2[d], Tonozwei[d], Vit-O_2[d], Vitozwei[d]	17590-01-1
Clobenzorex	4	*N*-[(2-Chlorophenyl)methyl]-α-methyl-benzeneethanamine; Asenlix, BA 7205, Dinintel, Finedal, Rexigen, SD-271-12	(±) 76553-22-5 (+) 13364-32-4
Ethylamphetamine	5	*N*-Ethyl-α–methyl-benzeneethanamine; Adiparthrol, Apetinil	457-87-4
Fenethylline	7	3,7-Dihydro-1,3-dimethyl-7-[2-[(1-methyl-2-phenylethyl)amino]ethyl]-1H-purine-2,6-dione; 7-Ethyltheophylline amphetamine, Amfetyline, Appine-V, BZT, Captagon, Fenetylin, Fitton, H-814, R-720-11	3736-08-1
Fenproporex	8	3-[(1-Methyl-2-phenylethyl)amino]-propanenitrile; Antiobes Retard, Appetitzugler, Dandi, Degadil, Delgafen, Desobesi, Diafanor, Dicel, Drenur, Falagan, Fenisec, Fenorex, Gacilin, Grasmin, Lebil, Lineal[e], Liofisan, Lipenan, Lipese, Lipofem, Lipoflex, Lipogen, Lipolin, Lipomax, Lipostil, N-2-cyanoethylamphetamine, Nilipoid, Perhoxene, Perphoxen, Perphoxene, Pesex R, Proporex, Solvolip, Suralgon, Tegisec	15686-61-0
Mefenorex[f]	9	*N*-(3-Chloropropyl)-α-methyl-benzeneethanamine; Doracil, Pondinil, Pondinol, Rondimen, RO-4-5282	17243-57-1
Mesocarb	11	3-(1-Methyl-2-phenylethyl)-*N*-(phenylaminocarbonyl)sydnoneimine; Fensidnimine, Sidnocarb, Sydnocarb, Sydnogluton[d]	34262-845
Prenylamine	14	*N*-(1-Methyl-2-phenylethyl)-γ-phenyl-benzenepropanamine; Angiovigor, Angormin, Angorsan , Bismethin, B-436, Carditin, Corontin, Corpax, Corosten, Crepasin, Daxauten, Elecor, Falicor, Herzcon, Hoechst-12512, Hostaginan, Incoran, Irrorin, Lactamine, Nyuple, Onlemin, Piboril, Prenylaminii, Prenylamin, Reocorin, Sedolatan, Segontin, Segontine, Synadrin, Valecor, Venaforte[d], Wasangor	390-64-7
Methamphetamine- (and amphetamine-) producing compounds			
Benzphetamine	15	*N*,α-Dimethyl-*N*-(phenylmethyl)-benzeneethanamine; Benzfetamine, Didrex , Inapetyl	156-08-1
Deprenyl	17	*N*,α-Dimethyl-*N*-2-propynyl-benzeneethanamine; Deprenalin, Deprenaline, Deprenil, Eldéprine, Eldepryl , Enprostil, E-250, Jumex, Jumexal, Movergan, Plurimen, Selegiline	(R) 14611-51-9 2323-36-6
Dimethylamphetamine	19	*N*,*N*-α-Trimethyl-benzeneethanamine; Dimephenopan, Metrotonin, Perneurin	4075-96-1
Famprofazone	20	4-Isopropyl-2-methyl-3-[*N*-methyl-N-(α-methyl-phenylethyl)-aminomethyl]-1-phenyl-3-pyrazolin-5-one; Gewodin[d]	22881-35-2
Fencamine	22	*N*-Methyl-*N*-(1-methyl-2-phenylethyl)-*N*'-3,7-dihydro-1,3,7-trimethyl-8-[[2- [methyl(1-methyl-2-phenylethyl)amino]ethyl]amino]-1H-purine-2,6-dione; Altimina, Altimine, Phencamine, Sicoclor, ST-374	28947-50-4
Furfenorex	23	*N*-Methyl-*N*-(1-methyl-2-phenylethyl)-2-furanmethanamine; Frugal, Frugalan, Furfurylmethylamphetamine	(±) 13445-60-8 (+) 3776-93-0

[a] This table represents names associated with the drugs described in this review. Names for drugs that are no longer available have been omitted when it was clear that the compound was no longer manufactured, as have names that are obviously the same drug under a slightly different name (i.e., Synadrin and Synadrin-60). If a related name is encountered, it is important to determine the actual structure of the drug to determine whether or not it is one of the precursor drugs. Structures 1–26 will assist in determining the drugs regardless of the name assigned.

[b] Other names were taken from articles referenced in this review or from general references [22,103,121].

[c] The Chemical Abstract Service (CAS) number refers to the compound itself. Other numbers may also apply to the drug in some other formulation (i.e., 390-64-7 is the CAS number for Prenylamine and 69-43-2 is the CAS number for Prenylamine Lactate). Only the numbers for the nascent drug are used.

[d] Multi-ingredient preparation that contains the drug as one constituent.

[e] Also used to refer to Diethylpropion.

[f] *The Merck Index* [121] lists Anexate as an alternate name for Mefenorex. Anexate is actually another name for Flumazenil, which is a benzodiazepine antagonist not associated with Mefenorex. This discrepancy was eliminated in the later version of the manual [22].

Table 2. Metabolic amphetamine and methamphetamine from precursor compounds[a]

Drug name and structure desig.		Percent of dose excreted Amph.	Methamph.	Subject	Ref.
Amphetamine-producing compounds					
Amphetaminil	3	3.3	NA[b]	Human	[100]
		+[c]	NA	Rat	[54]
Clobenzorex	4	5.5	NA	Rat	[48]
Ethylamphetamine	5	4.4–10.4	NA	Human[d,e]	[5]
		12.3–17.5	NA	Human[d,f]	[5]
		0.4–3.3	NA	Human[d,g]	[5]
		6.0–14.2	NA		
		5.1–7.1	NA		
		9.0–14.7	NA	Human[d,h]	[33]
		10	NA	Human	[9]
		+	NA	Human	[10]
		3.8	NA	Rat	[75]
		+	NA	Rabbit	[6]
Fenethylline	7	24.5	NA	Human	[35]
		4.7–15	NA	Human[d]	[89]
Fenproporex	8	27–31	NA	Human	[115]
		29–56	NA	Human	[9]
		+	NA	Rat[i]	[87]
Mefenorex	14	15	NA	Human	[16]
		+	NA	Rat[i]	[87]
Mesocarb	9	4	NA	Rat[d]	[96]
Prenylamine	11	2.5	NA	Human	[93]
		0.14	NA	Human	[34]
Methamphetamine- (and amphetamine-) producing compounds					
Benzphetamine	15	11.8	17.6	Human	[23]
		7.6–8.9	2.2–3.1	Human	[57]
		+	+	Human	[10,21]
		2.7	2.3	Rat	[90]
Deprenyl	17	5–22	36–63	Human	[101]
		5–7	11–16	Human	[63]
		3.2–24.5	6.4–68.9	Human	[36]
		+	+	Human	[62,80]
		18.5	28	Human	[104]
		+	NT[j]	Human[i]	[102]
		15–41	34–119	Human	[52]
		4.5–16.3	14.5–40.3	Human[d]	[106]
		8.7	20	Human[d,k]	[74]
		11.1	21.5		
		8	16		
		10.1	8.1	Dog	[105]
		5.2	4.2	Rat	[126]
Dimethylamphetamine	19	0.3	5.8	Rat	[58]
		1.3	11.3	Human	[58]
		20	16	Monkey	[113]
		+	+	Rabbit	[4]
		+	+	Human	[10]
Famprofazone	20	NT	6.2–18.7	Human[l]	[91]
		NT	12–57	Human[m]	[91]
		NT	17–38		
		NT	25–75		
		NT	+	Mouse	[85]
Fencamine	22		+	Human	[76]
Furfenorex	23	6.1–8.5	3.3–4.4	Human	[57]
		+	+	Human	[10]
		0.9	3.6	Rat	[60]

a Not all data are presented in this table. Generally, references that used only in vitro testing or those that did not indicate quantities were not used if other references containing such data did exist.
b NA: Not applicable — drug is not metabolized to methamphetamine.
c +: presence but not quantified.
d Measured for 24 h.
e Represents 20–36 mg dose with no control of urine pH.
f Represents 20-mg dose with urine acid pH controlled; *d*-, *d,l*-, and *l*-enantiomers administered respectively.
g Represents 20–36-mg dose with urine alkaline pH controlled.
h 30-mg Dose.
i Measured in brain.
j NT: Not tested.
k Represents 10-, 20-, and 30-mg dose, respectively.
l Measured for 72 h.
m Represents 100-, 50-, and 25-mg dose, respectively; percentages based on projections from 72 h measurements.

metabolites play in the action of deprenyl is not universally accepted, as evidenced by conflicting opinion in the literature that methamphetamine and amphetamine are not important factors in the action of this drug [36,52,111].

The question of action of methamphetamine and amphetamine in this case plays a role in the interpretation of analytical data associated with determination of drug use. The levels of methamphetamine and amphetamine are quite low compared to the initial deprenyl administered and since they are the *l*-enantiomer of the drugs, it is reasonably argued they do not play any significant role [52]. Amphetamine and methamphetamine are monoamine oxidase inhibitors. However, unlike deprenyl, the action of amphetamine and methamphetamine is more pronounced on the A rather than B form of the enzyme [112]. The inhibition caused by amphetamine and methamphetamine is a competitive and reversible phenomena, but the inhibition of monoamine oxidase caused by deprenyl is not reversible. Their low concentrations, even in long-term deprenyl therapy, is important to understand with respect to analytical test results, which show the presence of methamphetamine and amphetamine and the evaluation of the possibility of use of this drug as opposed to direct use of methamphetamine or amphetamine.

Deprenyl has also been shown to have significant positive effects in the prevention and treatment of Parkinson's disease-like symptoms associated with

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [29,53]. This protective effect is attributed to the enzyme inhibitory activity that prevents the oxidative conversion of MPTP by monoamine oxidase to the more toxic 1-methyl-4-phenylpyridinium (MPP+), which is suspected to be the causative agent in the MPTP associated symptoms [1]. This protective effect of deprenyl can, however, be overwhelmed by very high concentrations of MPTP [42]. Other medical uses for deprenyl are described later in this review.

Dimethylamphetamine is not available as a prescription drug and has no recognized medical use. It has been used in a number of studies targeted toward discovering the mechanism of action of amphetamines on the body and is available on the illicit market [58].

Ethylamphetamine is a schedule I drug in the U.S. and has no recognized valid medical use. It has been used elsewhere as an anorexic [22] and in a number of studies to help determine the mechanisms involved in the metabolism of amphetamine-like drugs [5–9,75].

Famprofazone is an antipyretic and analgesic that also has some slight sympathomimetic properties and is found as a component of the multi-ingredient medication, Gewodin [103]. The drug was recently removed from circulation in Korea because of its conversion to methamphetamine [91] but still remains available in Europe [103].

Fencamine is reported to be a central nervous system stimulant and has been used in the treatment of depression [103].

Fenethylline is a central nervous system stimulant and is used in the treatment of children with attention deficit disorders. It has also been used in the treatment of narcolepsy [103,107]. Although it has a significant central stimulant activity, the activity is not identical to that of amphetamine and the side effects associated with this drug are significantly less than those seen with amphetamine [71,89]. It has also been used as an antidepressant [71]. One of the advantages of this drug is the fact that it does not cause increased blood pressure often seen when using amphetamine, making it attractive for use in patients with cardiovascular difficulties [71].

The suggestion has been made that the activity of fenethylline is primarily due to the amphetamine rather than the fenethylline itself [35]. As with deprenyl, there is no debate that amphetamine is a metabolic product of fenethylline, but rather whether or not fenethylline has activity of its own. Subsequent evaluation of pharmacological data by Nickel et al. [89] showed however, that the activity associated with this drug closely mirrors the plasma concentrations of fenethylline and not amphetamine. Additionally, the pharmacological activities associated with the drug are different than those associated with amphetamine. Remembering that the amphetamine portion of the molecule is racemic, the activity expected to be observed would be less than that expected with an equivalent dose of *d*-amphetamine. Fenethylline is a schedule I drug in the U.S. and has no recognized valid medical use.

Fenproporex is an anorexic used in the short-term treatment of moderate to severe obesity [51,103,107].

Furfenorex is an anorexic used in the treatment of obesity [26,51,64].

Mefenorex is a sympathomimetic agent with properties similar to amphetamine, but has less effect on the cardiovascular system. It is used as an anorexic adjunct in the short-term treatment of moderate to severe obesity [51,103].

Mesocarb is a stimulant that does not have some of the negative side effects of amphetamine. It has been used to counteract the effects of benzodiazepines and has also been reported to increase workload capacity and cardiovascular function [118]. It has been shown to significantly increase learning ability [43] and has had significant positive influence on the excretion of epinephrine in hyperactive children [116]. It has also been used as a method to extend tolerance to low temperatures in both cold air (-20 °C) and cold water (0 – 2.5 °C). Even under these extreme conditions better overall thermal regulation was noted when the drug was used [2].

Prenylamine, a coronary vasodilator, is used in the treatment of angina [73]. It also functions as a calcium channel blocker [72,78] acting as a calcium antagonist [86]. Interestingly, it has also been shown to cause a dose-dependent decrease in anaphylactic histamine release in animals [44]. Recently, prenylamine was also shown to have a significant effect as an anti-tumor agent in the inhibition of cell proliferation in human colon cancer cells [3].

II. METABOLISM AND INTERPRETATION

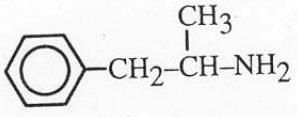
Important considerations for the interpretation of amphetamine and methamphetamine results include metabolism and excretion of the drugs and their metabolites. To the author's knowledge, there is no indication in any published research in this area that any of these drugs or their metabolites are racemized in the body. For this reason, knowledge of the configuration of the precursor drug is invaluable in the interpretation of results. Thus, a drug such as deprenyl, which is the *l*-enantiomer, gives rise to methamphetamine and amphetamine, which are also in the *l*-configuration.

However, enantiomeric configuration does influence the metabolism of amphetamine and methamphetamine,

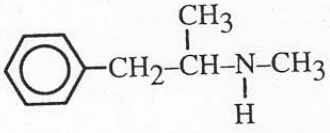
as well as the precursor drugs. When racemic methamphetamine or amphetamine is taken into the body, the *d*-enantiomer is metabolized more rapidly than the *l*-enantiomer. As a result, the composition of methamphetamine and its metabolite amphetamine in urine are not equally distributed. As time elapses following the administration of the drug, the enantiomeric distribution continues to change. The implications of these differences are discussed in the individual sections for the drugs to which they apply and the reader is referred to several other references for further information on this topic [4,24,25,27,55].

A. Amphetamine and Methamphetamine

The metabolism of amphetamine (Structure 1) and methamphetamine (Structure 2) has been extensively described in a number of publications [24,25,40]. The interpretation of amphetamine and methamphetamine results is complex due in large part to the influence of urinary pH on the excretion rate of these drugs [32]. Legitimate use of amphetamine and methamphetamine is accompanied by a valid medical prescription making interpretation straightforward. However, because of the nature of these drugs, having a legitimate prescription does not eliminate the potential for abuse. In fact, inappropriate medical use of the drugs can lead to dependence and ultimately to abuse. Even with a valid medical prescription, it is important to evaluate the enantiomeric composition of the drugs.



Structure 1. Amphetamine



Structure 2. Methamphetamine

Prescription methamphetamine is available only as the *d*-enantiomer. Therefore, the presence of both enantiomers could not come from use of prescription methamphetamine. Amphetamine, however, is prescribed as either the *d*-enantiomer or as the racemic *d,l*-mixture. In this case, interpretation of the enantiomeric composition is based on the composition of the prescribed drug. For example, if the prescribed drug was methamphetamine, the presence of both enantiomers is most likely due to the illicit use of racemic methamphetamine. If *d*-amphetamine was prescribed, then only the *d*-enantiomer should be seen. Likewise, if the racemic form was used, there should be clear evidence of the appropriate metabolic profile. Presence of methamphetamine in a sample from an individual for which amphetamine was prescribed is a clear indication of methamphetamine use since amphetamine is not metabolically converted to methamphetamine.

Although the Vicks Inhaler sold in the United States does contain *l*-methamphetamine, elsewhere in the world it does not. Therefore when evaluating enantiomeric results, it is important to check the Inhaler to ensure it actually contains the drug *l*-methamphetamine. For these reasons, interpretation of illicit use requires examination and evaluation of the enantiomers even if a prescription for the drug is available.

B. Precursor Compounds

1. General Considerations

For those precursor compounds that are excreted intact, the detection of the parent compounds when related to the amount of the amphetamine or methamphetamine present can be a powerful tool to help properly interpret the analytical results. In addition to the actual parent compound, there may be another metabolite that is unique to the compound and can be used to demonstrate the use of the precursor drug. These data combined with typical pharmacokinetic information can allow appropriate evaluation of the origin of amphetamine and/or methamphetamine.

Even if the presence of the parent precursor compounds cannot be demonstrated, there are analytical data that can be used to help evaluate the possibility of their use. For example, prescription deprenyl is the *l*-enantiomer. Therefore the methamphetamine and amphetamine metabolically produced from deprenyl are the *l*-enantiomers [106]. A finding of *d*-methamphetamine or the mixture of *d*- and *l*-methamphetamine would not be consistent with the administration of deprenyl.

Unfortunately, several of the drugs are metabolized to amphetamine and methamphetamine and are not detected in the urine. Fenproporex is an example of a compound that is essentially entirely metabolized to amphetamine. Studies of the excretion of the fenproporex in humans have shown very little of the parent drug excreted and even then only for a few hours, while the metabolite amphetamine could be detected for days [9]. Benzphetamine is another example of a precursor drug that cannot be detected in the urine following a single dose [23]. Inability to detect the parent drug has also been reported for amphetaminil [54], famprofazone [85,88,91], and deprenyl

[101,106] although several of these do produce unique metabolites.

From a forensic standpoint, it is important to consider the fact that these precursor drugs are typically controlled and, if legitimately available, can only be dispensed with a prescription. Lack of a valid medical prescription may have a strong influence on the interpretation of the presence of either amphetamine or methamphetamine. In addition, some of the drugs are for very specific medical conditions that are clearly demonstrable either by examination of the patient or by appropriate review of the medical records. Using the example of prenylamine, which is prescribed for angina, an individual who claims to have been prescribed the drug as a diet pill would not have a credible story.

Investigation of the pharmacological activity of several of these drugs is an active and ongoing process and their uses may change. As a result, it is important to maintain awareness of all reasonable clinical uses for these drugs. An example of the need to keep abreast of drugs' changing uses is deprenyl, which is used as a treatment of Parkinson's disease. If that were the only indication for the use of this drug, then simply knowing that the individual did not have Parkinson's disease would resolve the issue. Recent work, however, has shown deprenyl to be effective not only in the treatment of Parkinson's disease, but also in Alzheimer's disease [114], depression [15,53,65,74,77], prevention of stress ulcers [49], motion sickness [18], increased longevity in rats [67–70,82] as well as in man [13,14,65,66], and sexual activity in rats [69,70,125] and man [31,65,117]. The hypersexuality induced in man extended from virtually nonexistent to the point of being a problematical side effect in some patients [117]. The impact of deprenyl treatment on dementia has also been studied and shown by several investigators to have a significant positive effect [38,83,114].

As deprenyl and other precursor drugs come into wider use, the interpretation of amphetamine or methamphetamine positive results will require an even more thorough consideration of possible medicinal uses of these precursor drugs.

Many of these precursor compounds are relatively safe, but some are prone to be abused. Concern for the abuse potential of these drugs has caused some to be placed on the list of scheduled drugs or removed from the market [21,26,37,51,64,71,91,123,124]. There have also been reports of several of these drugs being associated with significant complications and, in several extreme cases, fatalities. For example, benzphetamine was determined to be the cause of death in a suicide case involving a young male [21] who showed high concentrations of the drug in blood, urine, and a variety of tissues. Clobenzorex has been shown to be responsible for cardiac arrest in at least one case, a woman who had a long history of taking (abusing) the drug [30]. Prenylamine has also been associated with dangerous ventricular arrhythmias [19,97]. These hazards are potentially useful information in the clinical emergency or postmortem environment.

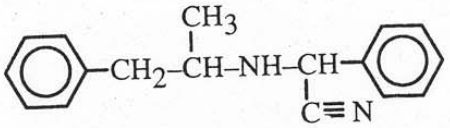
Examination of the chemical structure of these compounds (see next two sections) reveals the portion of the molecule that gives rise to either amphetamine (amphetaminil, clobenzorex, ethylamphetamine, fenethylline, fenproporex, mefenorex, mesocarb, prenylamine) or methamphetamine (benzphetamine, deprenyl, dimethylamphetamine, famprofazone, fencamine, furfenorex). As expected, the methamphetamine derived from these drugs is subsequently metabolized to amphetamine.

A number of studies have examined the extent of conversion of these compounds to amphetamine or methamphetamine. These data are summarized in Table 2. Examination of data presented in this table shows substantial variability. While there are a number of possible reasons for this variability, the most likely is the fact that urine pH has such a significant effect on the rate of excretion of amphetamine and methamphetamine. In most of the cited studies, there was no attempt to control the urine pH of the experimental subjects. One exception to that lack of control is seen in the study by Elsworth et al. [36], which did take into account the effects of pH. Their findings, as expected, indicated that urine pH had a significant effect on the excretion of the drugs. The excretion of amphetamine and methamphetamine is also dramatically affected by adjustment of urine pH. While the lack of control of urine pH is unfortunate from a pharmacokinetic standpoint, from a forensic perspective the data probably represent the variability one would likely see in typical samples submitted for analysis.

2. Amphetamine-Producing Drugs

Amphetaminil (Structure 3). Studies have shown that amphetaminil is not detected in the urine after administration of the drug to humans [12,100] or rats [54]. Amphetamine levels measured in blood accounted for only 1–2% of the dose while the brain was shown to contain two to three times the amount of amphetamine found in blood. Adipose tissue also contained higher levels of amphetaminil than the blood. But in this tissue, much of the drug was still intact. It was therefore assumed that adipose tissue was a temporary depot for the highly lipophilic drug, whereas the brain was a site of degradation to amphetamine. Concentrations of amphetamine also closely correlated

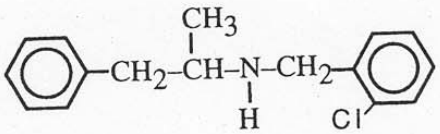
vith the pharmacological activity of this drug. After only 30 min, two thirds of the amphetaminil was already degraded to amphetamine.



Structure 3. Amphetaminil

Extraction of amphetaminil from blood, brain, and adipose tissue was accomplished using benzene after adjustment of the pH to 5. Amphetamine is readily extracted at alkaline pH, into an organic solvent. Therefore separate extraction conditions must be used to isolate both amphetamine and amphetaminil from the same sample. A consideration in the analysis of amphetaminil is the instability of the drug in polar solvents. Substantial degradation of the drug was noted in such solvents, however use of non-polar, nonaqueous solvents eliminated the decomposition problem [54].

Clobenzorex (Structure 4). The metabolism of clobenzorex has been studied in rats using the radiolabeled drug [48]. In this study, 4-hydroxyamphetamine, 4-hydroxyclobenzorex, clobenzorex, amphetamine, and hippuric acid were found. Significant amounts of the hydroxy forms were conjugated as demonstrated by changes in their chromatographic behavior following hydrolysis.



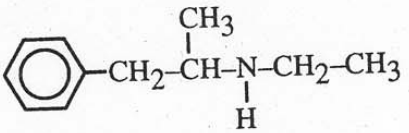
Structure 4. Clobenzorex

Separation of the compounds was accomplished by extraction of the amphetamine at pH 10 – 11 into diethyl ether and the hippuric acid at pH 1 – 2 into chloroform. The clobenzorex, hydroxyclobenzorex, and hydroxyamphetamine were then extracted following hydrolysis to free the conjugates. Amphetamine accounted for approximately 5% of the initial dose and 4-hydroxyamphetamine for another 3% in the first 24 h. Thirty percent of the dose was recovered as clobenzorex or hydroxyclobenzorex in the same time period.

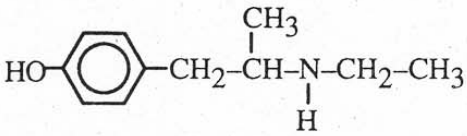
Clobenzorex is prescribed as the racemic drug [51]. The *d*-enantiomer shows the most pharmacological activity, similar to amphetamine and methamphetamine with respect to the enantiomeric pharmacological activity. Since the drug is racemic, the product amphetamine is also racemic. While this alone cannot absolutely differentiate whether or not the amphetamine originated from this precursor, it can eliminate the possibility of this drug as the origin if the amphetamine found is only the *d*-enantiomer.

A gas chromatography/mass spectrometry (GC/MS) procedure for the analysis of a number of drugs, including clobenzorex, from urine using a C-18 solid-phase extraction method has been reported that involved elution of the drugs with chloroform:isopropanol followed by derivatization and analysis [41]. The quantitation limits for the drugs in this procedure were 200 ng/mL for derivatized compounds and 500 ng/mL for underivatizable compounds.

Ethylamphetamine (Structure 5). Ethylamphetamine is excreted intact and metabolized to amphetamine and 4-hydroxyethylamphetamine (Structure 6) [75]. Following administration of a 30 mg dose, 9 – 14.5% of the dose was excreted as amphetamine. When the drug was administered as a slow release formulation, the amounts found were comparable (12.4 – 14.7%) [33]. In both cases, the urine pH was monitored but not adjusted. The same study evaluated the excretion of the drugs following use of a diuretic. After use of acetazolamide, a carbonic anhydrase inhibitor, and clofenamide, the percentages of amphetamine excreted were 8.5 – 16.3% and 8.2 – 16.4% respectively. While these numbers do not dramatically differ from those without diuretics, there was a significant difference in the excretion profile. With both of these diuretics, the levels of detectable drugs were significantly diminished and, in at least one subject, no detectable amphetamine was seen at 12 h post dose with acetazolamide. Significantly lower percentages were seen for the other subjects. Substantially lower percentages were also observed at 12 h with clofenamide, although some amphetamine could be detected in all subjects. Use of the diuretic furosemide did not diminish the amount of detectable drugs at the 12-h point as seen with the other diuretics. In all cases, detection of ethylamphetamine and amphetamine was possible in urine samples 72 h following the administration of the drug. Detectability of the drug was affected to some extent by the use of the diuretics, which has some potential impact on workplace and sports testing, a consideration in the process and timing of sample collection.



Structure 5. Ethylamphetamine

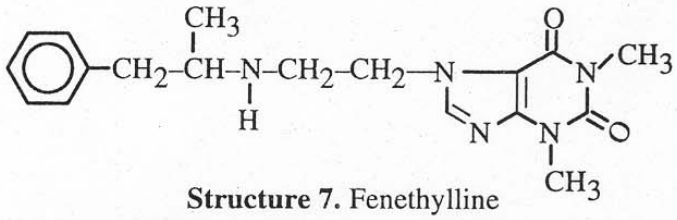


Structure 6. 4-Hydroxyethylamphetamine — a metabolite of ethylamphetamine

Significant differences were noted in the metabolism of ethylamphetamine depending on the enantiomer administered to humans [5]. Under controlled urine pH conditions, the *d*-enantiomer was metabolized much more rapidly than the *l*-enantiomer. In all cases, the amount of ethylamphetamine exceeded the amount of amphetamine excreted. In the first 24 h, the ratio of ethylamphetamine to amphetamine was approximately 1.3:1 after administration of *d*-ethylamphetamine; 5:1 after administration of racemic ethylamphetamine; and approximately 12:1 following administration of the *l*-enantiomer owing to the rapid metabolism of the *d*-enantiomer. The presence of the parent drug and the even higher concentration of the hydroxylated metabolite make determination of the use of ethylamphetamine relatively easy compared to some of the other precursor compounds.

Extraction of ethylamphetamine, amphetamine and 4-hydroxyethylamphetamine has been accomplished from hydrolyzed urine at pH 11 with ethyl acetate:methylene chloride (1:1) giving recoveries for all three compounds between 75% and 85%. The pH of ethylamphetamine was reported to be 10.23, requiring the sample pK to be adjusted higher than ordinarily required for amphetamine or methamphetamine to neutralize the charge on the amine group, thus allowing efficient extraction into an organic solvent [120]. The extract was then evaporated and derivatized with heptafluorobutyric anhydride. GC/MS analysis was accomplished on an OV-17 packed column or 25 m 5% phenylmethyl silicone capillary column using either electron ionization or isobutane chemical ionization [75].

Fenethylline (Structure 7). Using radiolabeled fenethylline, 24.5% of the dose was shown to be excreted as amphetamine, 27.2% as hippuric acid and 6.6% as 4-hydroxyamphetamine. A relatively small amount of the drug (3.6%) was excreted intact. There was a statistically significant difference in the amount of hippuric acid formed from fenethylline compared to an equivalent dose of amphetamine [35]. While this is metabolically interesting, it is of less practical value in assessing the use of this drug versus amphetamine in a single biological sample since hippuric acid is a breakdown product of a number of different compounds.



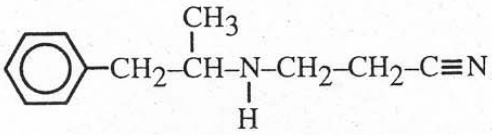
Structure 7. Fenethylline

Fenethylline is racemic for the amphetamine portion of the molecule, therefore enantiomer analysis can be a significant aid in interpretation of amphetamine positive data. In addition, another major metabolite formed after cleavage of the fenethylline molecule is theophylline.

Theophylline and several of its metabolites are also found in urine following administration of this drug [35,89]. Ellison et al. [35] measured theophylline to be 13.7% of the dose in the first 24 h. Use of thin layer chromatography (TLC) to detect the drug and its metabolites is described and was facilitated by the use of radiolabeled ^{3}H-fenethylline. Two different labeled forms of the drug were used, one with the tritium label on the amphetamine portion and another with the label on the theophylline portion of the molecule [35]. High performance liquid chromatography (HPLC) was used with ultraviolet (UV) and fluorescent detection following a simple solvent extraction to identify many of the different metabolites of this drug [89]. Theophylline is readily measured and can be useful in the interpretation of the metabolism of fenethylline. Although some disagreement exists concerning the pharmacology of fenethylline relating to the effect of the drug itself, rather than its metabolic product amphetamine [89], there is no disagreement concerning the production of amphetamine. Fenethylline does not show the same pharmacological activity as amphetamine, most notably with respect to the effects on the heart [71]. The combination of racemic amphetamine and the presence of theophylline allows identification of this precursor drug from the use of amphetamine alone.

Fenproporex (Structure 8). Studies of the excretion of fenproporex in man have shown very little of the parent drug excreted and only for a few hours, while the metabolite amphetamine could be detected for days [9]. Under acid urine conditions, between 5.4% and 8.7% of the drug was excreted intact. However without control of the urine pH, only about 3% of the dose was excreted intact and could not be detected for more than 3 hrs post-dose (n = 2). Studies have also demonstrated that the amphetamine excretion was essentially identical to that seen with the administration of a nearly equal dose of amphetamine [9,115]. In the case of fenproporex, very little could be determined concerning the origin of the drug from analytical results unless the enantiomeric composition was deter-

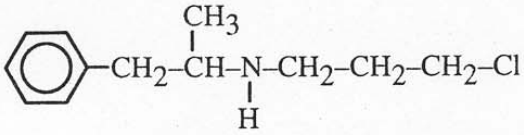
mined. With that information, it would be possible to determine whether or not the urine metabolites were consistent with the use of the prescribed drug.



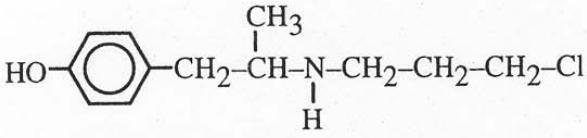
Structure 8. Fenproporex

The drug has been extracted with ether from alkalinized urine followed by derivatization with acetic anhydride and analysis by GC [9].

Mefenorex (Structure 9). Mefenorex has been demonstrated to be excreted intact in a number of different animals. The percentage of intact drug excreted varied considerably between species with only 1% excreted in the rat and human, 3% in the Guinea pig, 17% in the dog, and 18% in the rabbit [120]. A study by Blum [16] did not detect any of the intact drug excreted from humans. Several metabolites were described however, including 4-hydroxymefenorex (Structure 10) as well as small amounts of 4-hydroxyamphetamine and 4-hydroxynorephedrine. The 4-hydroxymefenorex is a useful indicator because it is unique to the drug and is found at much higher concentrations than the parent. Normally, aromatic hydroxylations of *N*-substituted amphetamines are only a minor pathway in humans. The hydroxylation of mefenorex at the 4 position, however, was reported to be 37% of the initial dose [120].



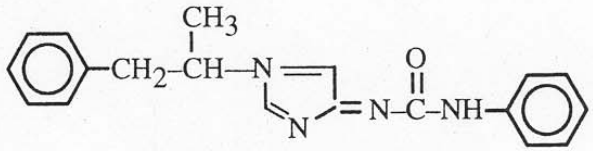
Structure 9. Mefenorex



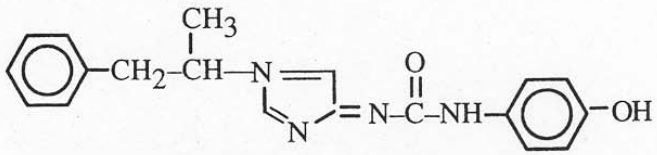
Structure 10. 4-Hydroxymefenorex — a metabolite of mefenorex

Nazarali et al. [87] described a procedure for the analysis of mefenorex in brain tissue using GC with electron capture detection of the pentafluorobenzoyl derivative on an OV-101 packed column. A full scan GC/MS procedure has been described for the analysis of mefenorex, and several other drugs, from urine using a solid-phase extraction method. The extraction was accomplished by passing the sample through a C-18 column followed by elution with chloroform:isopropanol [41]. The quantitation limits for the drugs were 200 ng/mL for derivatized compounds and 500 ng/mL for underivatizable compounds. Given the low levels of intact drug excreted in urine following administration of this drug this procedure would have limited utility.

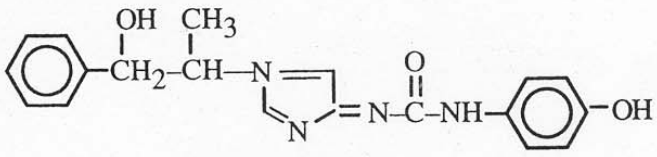
Mesocarb (Structure 11). Mesocarb is excreted in only trace amounts, but both mono (Structure 12) and dihydroxy (Structure 13) metabolites were found in the urine. Efficient detection of these hydroxylated metabolites requires hydrolysis prior to extraction. In the rat, the amount of the dihydroxy metabolites in the free, mono, and diconjugated forms accounted for 40% of the administered dose. The hydroxy metabolite accounted for another 22% of the administered dose while the intact drug was only 1% and the product amphetamine only 4% of the administered dose [96].



Structure 11. Mesocarb



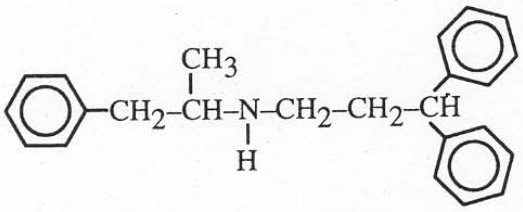
Structure 12. Hydroxymesocarb — a metabolite of mesocarb



Structure 13. Dihydroxymesocarb — a metabolite of mesocarb

Analysis was accomplished by solid-phase extraction of the drug and metabolites at pH 9.0 on XAD-2 resin, washing with water, then eluting with methanol. Isobutane chemical ionization was accomplished to identify the metabolites and electron ionization GC/MS of the isothiocyanate derivative was accomplished on a 2% OV-1 packed column.

Prenylamine (Structure 14). Prescribed prenylamine is a racemic mixture consisting of both enantiomers. Its metabolism has been shown to be enantioselective [45,92,99] as has its disposition [47]. This fact can be of tremendous assistance in the interpretation of the origin of amphetamines. Since prenylamine is a racemic mixture, both the *d*- and *l*-enantiomers of amphetamine would be found in urine. The complicating part of this interpretation comes from the fact that the metabolism of *d*-prenylamine is more rapid than *l*-prenylamine. As a result, the *d*-metabolites would be excreted more rapidly than the *l*-enantiomers. Determination of prenylamine in plasma showed that the amount of *l*-prenylamine exceeded the amount of the *d*-enantiomer by four to one [108]. Another study also indicated the *d*-enantiomer is metabolized more rapidly than the *l*-form. Although doubled, the difference was not as great [46]. It is reasonable to assume, therefore, that more of the product amphetamine would be the *d*-enantiomer than the *l*-form initially. This is similar to what is seen with the metabolism of amphetamine and methamphetamine. In addition to amphetamine [34,93], 4-hydroxyamphetamine, norephedrine, 4-hydroxynorephedrine [93], and dipheny-propylamine were identified as metabolites [34].



Structure 14. Prenylamine

A number of different methods have been developed for the analysis of prenylamine. These methods include TLC [93], HPLC [45,46], and GC/MS [108]. The excretion of amphetamine following the administration of 180 mg of prenylamine was equivalent to the amount of amphetamine excreted following a 2 mg dose of amphetamine [93].

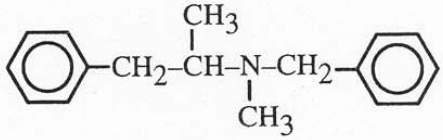
A total of 45.9 g of a 200-mg dose was excreted as unchanged prenylamine [45]. The distribution of the prenylamine was in both free and conjugated forms, with slightly more than half in the conjugated form. Schmidt et al. [108] described a procedure for the extraction and analysis of the drug from acidified plasma by taking a 1 mL sample and extracting the drug with 5 mL methylene chloride followed by washing with 2 mL 0.1 M NaOH solution. The dried extract was then derivatized with pentafluoroproprionic anhydride (PFPA) then analyzed by GC/MS with a 25-m 5% phenylmethyl silicone column. Electron ionization at 20 eV was used and the method demonstrated a detection limit of 0.2 ng/mL, which was 10 times more sensitive than a previously reported HPLC assay.

A GC/MS procedure for the analysis of prenylamine and several other drugs from urine using solid-phase extraction on a C-18 column has been reported [41]. The drug was eluted from the column using chloroform: isopropanol followed by derivatization and GC/MS analysis. The quantitation limits for the drugs in this study were 200 ng/mL for derivatized compounds and 500 ng/mL for underivatizable compounds.

HPLC analysis of prenylamine from plasma and urine was conducted using a C-18 column following either alkaline or ion-pair extraction. Derivatization of the compound with R-napthylethyl isocyanate allowed separation of the enantiomers and, due to the strong fluorescence of the derivative, allowed detection of as little as 2 ng/mL of either enantiomer of prenylamine in urine [46].

3. Methamphetamine- (and Amphetamine-) Producing Drugs

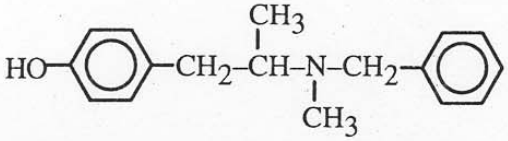
Benzphetamine (Structure 15). The metabolism of benzphetamine is nearly complete with little, if any, of the drug excreted in the urine unchanged. The intact drug has been reported in some studies [10,57] but not in others [23]. A reasonable explanation for the difference in these reports is that the GC method used by Budd and Jain [23] had a detection limit for benzphetamine of 150 ng/mL using a flame ionization detector while Inoue and Suzuki [57] used isobutane chemical ionization mass spectrometry with a much lower detection limit. In addition, the study by Budd and Jain [23] involved only the administration of a single 20 mg dose of benzphetamine while benzphetamine prescriptions are typically for either 25 mg or 50 mg tablets taken one to three times daily for up to several weeks. Since the pH of benzphetamine has been determined to be 6.55, it is likely that little of the drug would be excreted intact [119].



Structure 15. Benzphetamine

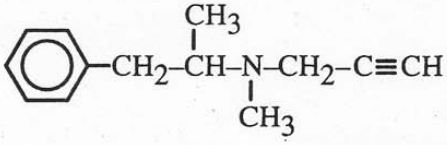
A GC/MS procedure for analysis of benzphetamine and several other drugs from urine using a C-18 solid-phase extraction method has been reported. After application of the sample on to the extraction column, the drugs were

eluted with chloroform:isopropanol [41]. The limit of quantitation for the drugs was 200 ng/mL for derivatized compounds and 500 ng/mL for underivatizable compounds, a high concentration for a drug-like benzphetamine that is usually found only at a low concentration and for a short period of time. The metabolic profile for this drug is much the same in humans as in rats with only one metabolite found in rats that was not found in humans. Of the various metabolites identified, 1-(4-hydroxyphenyl)-2-(*N*-methyl-*N*-benzylamino) propane (Structure 16) was found to be unique and characteristic of the use of benzphetamine [57]. It was also excreted at levels equal to, and in most cases, higher than, those of methamphetamine or amphetamine. As a result, sensitivity of the detection method is not a significant problem for this analyte. Much of the 1-(4-hydroxyphenyl)-2-(*N*-methyl-*N*-benzylamino)propane was excreted as the glucuronide conjugate. Between 5% and 6% of the dose was excreted as the free metabolite, while another 14 – 28% was excreted as the glucuronide conjugate [57]. The benzphetamine metabolites were incubated at pH 5.0 for 48 h at 37 °C with β-glucuronidase to hydrolyze the conjugates. The sample was then made alkaline (pH 9.0) by the addition of Na_2CO_3 then extracted into chloroform:isopropanol (3:1), which gave recoveries of 96 – 100%. Unfortunately, samples tested for amphetamine and methamphetamine are typically not hydrolyzed, therefore an additional hydrolysis step must be added to recover the majority of this metabolite.

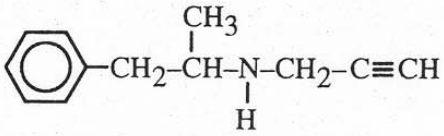


Structure 16. 1-(4-Hydroxyphenyl)-2-(*N*-methyl-*N*-benzylamino)propane — a metabolite of benzphetamine

Deprenyl (Structure 17). Deprenyl has been shown to lead to the production of methamphetamine, amphetamine, and desmethyldeprenyl (Structure 18) [52,80]. Desmethyldeprenyl can be detected in urine, at least for a short time, and its presence can clearly demonstrate the use of deprenyl. The metabolism of deprenyl to desmethyldeprenyl has been reported in a number of different studies. Unfortunately, the extent of conversion of the drug has not been quantified in many of these reports.



Structure 17. Deprenyl



Structure 18. Desmethyldeprenyl — a metabolite of deprenyl

Analysis of desmethyldeprenyl has been described by a number of different methods including packed and capillary GC, as well as GC/MS. Salonen [105] found 0.03% and 0.01% of 3 mg/kg and 10 mg/kg doses administered to dogs as desmethyldeprenyl. The percentages of amphetamine (10.1% and 8.1%), and methamphetamine (2.4% and 4.5%) for the same doses indicate the amount of desmethyldeprenyl excreted is small compared to the other metabolites. Measuring plasma levels of amphetamine, methamphetamine, and desmethyldeprenyl showed the desmethyldeprenyl level dropped below those of amphetamine and methamphetamine in less than 10 h after administration [98]. In a postmortem case involving deprenyl, femoral blood levels for amphetamine and methamphetamine were 70 ng/mL and 170 ng/mL respectively, which was noted as being four times the concentration listed by the manufacturer for serum levels of the drug during clinical trials [80]. Administration of a 10 mg dose to a healthy male volunteer led to peak plasma concentrations of approximately 4 ng/mL of amphetamine and 12 ng/mL of methamphetamine [98].

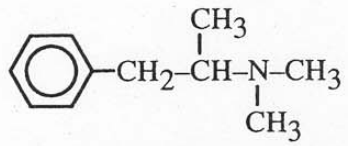
The most significant characteristic of deprenyl from a forensic standpoint is the fact that the drug is the *l*-enantiomer, therefore all of the metabolites are also the *l*-enantiomer. There is no indication that any racemization occurs with deprenyl during metabolism [106]. As a result, methamphetamine and amphetamine resulting from the metabolism of deprenyl would not likely screen positive by most immunoassay systems.

Routine GC/MS analysis cannot differentiate between the methamphetamine enantiomers. However differentiation of the enantiomers is possible using readily available chiral columns or derivatizing reagents either by GC/MS or HPLC [27]. Such evaluation is an important part of interpretation of methamphetamine results due to the commonly used Vicks Inhaler, which contains 50 mg of *l*-methamphetamine [28,39,55,110].

Analysis of desmethyldeprenyl has been accomplished by extraction of the drug from plasma by addition of NaOH and Triton X-100 (to release the bound fraction of the drug) followed by 6 mL of toluene. After shaking, the organic layer was removed and the drug back-extracted into 1 mL of 1.0 M HCl solution. Sodium chloride and 0.5 mL 1.0 M NaOH were then added and the drug was re-extracted into 0.1 mL toluene followed by derivatization with heptafluorobutyric anhydride (HFBA). Negative ion

chemical ionization GC/MS analysis gave detection limits of 0.25 ng/mL of desmethyldeprenyl [98]. Another method employed electron capture detection of the trichloroacetyl derivative following extraction of 0.5 mL of plasma or urine with hexane. This procedure gave a detection limit of 3 ng/mL (S/N 3:1) [105].

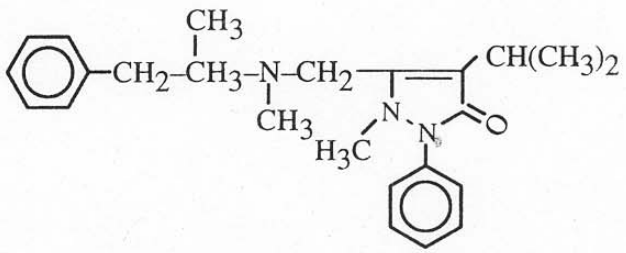
Dimethylamphetamine (Structure 19). Dimethylamphetamine is not available as a prescription drug and has no recognized medical use. Therefore it would be reasonably easy to determine that its presence was from illicit use. It has no advantage over the use of methamphetamine. In fact it has less pharmacological effect than methamphetamine. It does, however, make interpretation of the results relatively easy when considering the illicit nature of use. If it is present, its use is illicit. If only the metabolic product methamphetamine is measured, absent valid medical prescription, the use is illicit. Metabolism of dimethylamphetamine has been studied both in rats and humans [4,58]. The metabolic pattern is very similar for both species with the expected differences in aromatic hydroxylation being more pronounced in the rat. The major excretion products of dimethylamphetamine in humans are dimethylamphetamine and dimethylamphetamine-*N*-oxide making up an average of 15.6% and 21.7% of the initial dose, respectively, during the first 24 h as compared to 7.5% for methamphetamine and 0.65% for amphetamine. From 24 to 72 h, methamphetamine was the most prominent metabolite found, although dimethylamphetamine, dimethylamphetamine-*N*-oxide and the 4-hydroxy forms of dimethylamphetamine and methamphetamine were also seen.



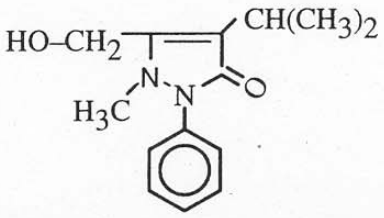
Structure 19. Dimethylamphetamine

Extraction of dimethylamphetamine has been accomplished from alkaline urine using diethyl ether. Following back extraction into 0.2 M HCl, the solution was again made basic and the drug re-extracted into diethyl ether. The *N*-oxide form of the drug was measured following reduction to dimethylamphetamine and subsequent extraction and analysis. To determine the hydroxylated metabolites, the samples were incubated with β-glucuronidase prior to extraction. Efficiencies of extraction were 97 – 100% and analysis was accomplished on a GC column of 2% apiezon/5% KOH for the free base and 3% OV-17 for the trifluoroacetyl and trimethylsilyl derivatives. Chemical ionization mass spectral analysis was accomplished with isobutane as the reagent gas [58].

Famprofazone (Structure 20). Following administration, famprofazone was not detected in urine either as the free drug or as a hydroxylated metabolite. When metabolized to methamphetamine, famprofazone also yields 3-hydroxymethylpyrazolone (Structure 21), which is subsequently excreted in the urine. The 3-hydroxymethylpyrazolone is essentially 100% conjugated and must therefore be hydrolyzed prior to analysis by GC/MS. Detecting the presence of 3-hydroxymethylpyrazolone is a clear indication of the use of famprofazone [88]. Mrongovius et al. [85] found that 3-hydroxymethylpyrazolone was always found in urine when methamphetamine was seen.



Structure 20. Famprofazone

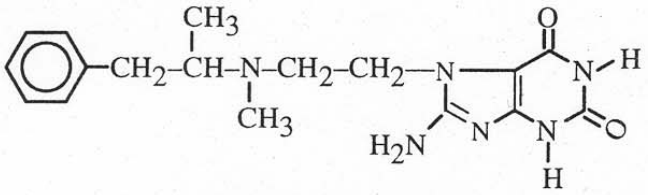


Structure 21. 3-Hydroxymethylpyrazolone — a metabolite of famprofazone

The 3-hydroxymethylpyrazolone was extracted from urine by using Extrelut solid-phase extraction cartridges after hydrolysis with aryl sulfatase and β-glucuronidase. After adjustment to an alkaline pH using ammonium buffer, the metabolite was eluted with chloroform. GC/MS analysis was accomplished on a 20 m SE-30 capillary column [85]. Similar but alternative GC/MS methods have been described in several other studies [88,91].

Fencamine (Structure 22). The excretion of fencamine was studied in rats and humans by Mallol et al. [76]. The identification of the drug and metabolites was accomplished with TLC and colorimetry. Intact fencamine could be detected for 48 hrs following a 50 mg oral dose of the drug to humans. Peak concentrations of the drug in urine were seen less than 3 hrs following administration. Approximately 32% of the dose was excreted as the intact

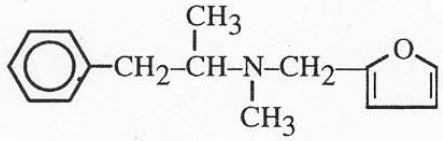
drug in 48 hrs and 26.6% in the first 24 hrs in humans (eight subjects). Excretion of fencamine was affected by adjusting urine pH. In the rat, for example, acidification of the urine increased the rate of excretion 2.5 fold.



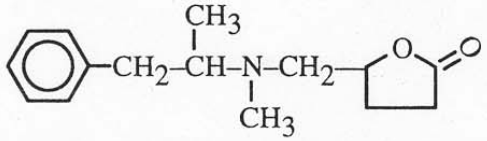
Structure 22. Fencamine

Since fencamine is administered as the *d,l*-mixture, the resultant amphetamine would also be racemic. Evaluation of the amphetamine enantiomer composition would therefore be of substantial assistance in interpretation of results with respect to the possibility of the amphetamine having been derived from fencamine.

Furfenorex (Structure 23). The metabolism of furfenorex is nearly complete with very little, if any, of the parent drug excreted in the urine unchanged. The metabolic profile for this drug is less complex in humans than in rats, but still yields a number of different metabolites. Of the various metabolites identified, 1-phenyl-2-(*N*-methyl-*N*-γ-valerolactonylamino)propane (Structure 24) was found to be unique and characteristic of the use of furfenorex [57]. It was also excreted at levels higher than the metabolites methamphetamine or amphetamine. Therefore sensitivity of the detection method in this case is not a significant problem.



Structure 23. Furfenorex

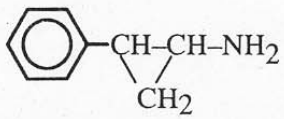


Structure 24. 1-Phenyl-2-(*N*-methyl-*N*-γ-valerolactonyl-amino)propane — a metabolite of furfenorex

In order to extract this metabolite efficiently from urine, however, it is necessary to use an acid rather than a basic extraction. Extraction at pH 3.5 yielded 10 fold higher recovery of 1-phenyl-2-(*N*-methyl-*N*-γ-valerolactonylamino)propane compared to a basic extraction [60]. This metabolite was extracted from acidified urine (pH 3.5) by washing several times with diethyl ether followed by extraction into chloroform:isopropanol (3:1) giving recoveries of 96 – 100%. Unfortunately, since amphetamine and methamphetamine are typically extracted under basic conditions, it would require a separate procedure in order to extract the metabolite. Identification of this compound would clearly demonstrate furfenorex as the origin of amphetamine and methamphetamine.

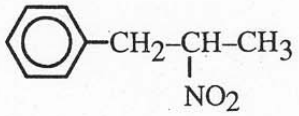
III. OTHER SOURCES

Tranylcypromine (parnate) (Structure 25), a monoamine oxidase inhibitor, has been reported as a metabolic source of amphetamine. Unlike the other drugs described in this review, there is considerable controversy concerning this matter. At the present time, scientific data indicates that measurable amounts of amphetamine are not produced from the administration of tranylcypromine [61]. Since the evidence for the formation of amphetamine from this drug is anecdotal at this time, it is most reasonably considered not to be a metabolic source of amphetamine until a definitive study can demonstrate its presence.



Structure 25. Tranylcypromine

In addition to the compounds mentioned above, there is another possible source of amphetamine that is not the result of consumption of amphetamine by an individual. 1-phenyl-2-nitropropane (Structure 26) has been shown to be converted to amphetamine by 12 different anaerobic intestinal bacteria [84]. In this study, a racemic mixture of 1-phenyl-2-nitropropane was incubated with the bacteria and the resultant amphetamine analyzed. All of the amphetamine formed by these microorganisms was the *l*-enantiomer, thereby demonstrating the stereospecific activity of the microbial enzymes with respect to this drug. While this phenomena has clearly been demonstrated, as has the fact that nitroalkanes are found in the human digestive tracts, it is unlikely the amount of amphetamine formed would be of clinical or forensic consequence.



Structure 26. 1-Phenyl-2-nitropropane

CONCLUSION

The presence of methamphetamine or amphetamine in a biological sample can have significant import to the individual from whom the sample was taken. The potential for misinterpretation of these results takes on dramatic importance in those circumstances where the results have a significant impact on the individual. Knowledge of the potential origins of amphetamine and methamphetamine in biological samples holds an important place in the area of forensic toxicology. In a clinical emergency setting, it can be important to prevent misinterpretation of the situation and may therefore alter treatment. In workplace drug testing, it can mean the difference between punitive action and no action being taken, and in the postmortem arena it can be important in evaluation of the potential cause of death. This information is also important to programs that focus on driving under the influence because the presence of these drugs may indicate abuse or legitimate medical use.

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ABOUT THE AUTHOR
J. T. Cody

John T. Cody is currently Deputy Director of the Clinical Investigation Directorate at Wilford Hall Medical Center, which conducts research in a wide variety of medically-related areas. He is also the consultant to the Air Force Surgeon General for Drug Testing. He received a B.A. degree from Iowa Wesleyan College with majors in biology and physical education. He was awarded M.S. and Ph.D. degrees from the University of Iowa where his graduate studies encompassed both chemistry and science education. Dr. Cody's dissertation was on the investigation of an enzyme mechanism.

Dr. Cody was previously Deputy Director of the Air Force Drug Testing Laboratory, which tests specimens from service members for drugs of abuse throughout the world. His special research interests center on drug metabolism, stability, and the influence of various factors affecting drug analysis. He is also deeply involved in computer-assisted analysis of GC/MS data. He is a certified laboratory inspector for the National Laboratory Certification Program coordinated by the Department of Health and Human Services.