II.2.1 Amphetamines and their metabolites

By Nariaki Takayama and Kazuichi Hayakawa

Introduction

Amphetamines are a group of drugs stimulating the central nervous system; they act on the cerebral cortex to enhance psychic activities, resulting in the removal of general fatigue and drowsiness and thus in the transient improvement of working efficiency. Their abuse causes dependence, hallucination, delusion and changes in personality. Because of such harmfulness of the drugs, their use and possession are prohibited by the Stimulant Drugs Control Law in Japan [1]. The recent methamphetamine (MA) abuse is characteristically involving young generation, and causing a serious social problem; it is regarded as the 3rd peak period of MA abuse [2]. The drug is being smuggled from China, Korea Peninsula and the so-called “Golden Triangular Zone” [3], where borders of Myanmar, Thailand and Laos are intercrossing.

The stimulant drugs include amphetamine (AP, 1-phenyl-2-aminopropane), MA (1-phenyl-2-methylaminopropane) and their salts. As an ethical drug for treatment of depression, only MA hydrochloride (commercial name: Philopon) is available from Dainippon Pharmaceutical Co., Ltd., Osaka in Japan. Most of MA being abused is the one smuggled from abroad. In the Stimulant Drugs Control Law, dimethylamphetamine (DMA, 1-phenyl-2-dimethylaminopropane), deprenyl (N-α-dimethyl-N-2-propynylphenethylamine), ephedrine, phenylpropanolamine (racemic norephedrine), methylephedrine, chloroephedrine, chloromethylephedrine, phenylacetic acid, phenylacetoacetonitrile, phenylacetone are also being controlled as materials for producing MA [2] (Figure 1.1).

Unchanged MA, its metabolite AP and \( p \)-hydroxymethamphetamine (\( p \)OHMA) are usually detected from urine of MA abusers. Recently, the abuse of DMA, a material for producing amphetamines, has been reported; DMA is partly metabolized into MA, AP and \( p \)OHMA, which are excreted into urine together with unchanged DMA [4, 5]. Therefore, it is now essential to test the presence of DMA\(^3\) for urine of abusers in order to discriminate between DMA and MA abusers. Benzphetamine (BZP) is commercially available in USA as a slimming drug (Didrex); a major part of the drug is metabolized into 1-(\( p \)-hydroxyphenyl)-2-(\( N \)-benzylamino)propane (OHnorBZP), and a minor part of it into MA, which are both excreted into urine. Thus, the detection of OHnorBZP has also become required for urine specimens of MA abusers [6, 7].

The optical isomers of MA exist, because of the presence of asymmetric carbon in the MA structure. The medical drug Philopon is the \( d \)-isomer of MA. MA being abused is largely its \( d \)-form, but the \( l \)-form has occasionally become detectable from specimens of abusers [8]. However, according to the Control Law in Japan, the optical isomers are not discriminated; both \( d \)- and \( l \)-forms are the objects of legal control. The effective ingredient of a nasal decongestant Vicks Inhaler, being sold in U.S.A., is \( l \)-MA. Selegiline (\( l \)-deprenyl, FP\(^®\), Fujimoto Pharmaceutical, Osaka, Japan) started to be used for treatment of Parkinson’s disease from...
Amphetamines and their metabolites

December, 1998 in Japan; it is metabolized into $l$-MA followed by $l$-AP to be excreted into urine [9]. Famprofazone (Figure 1.1), an effective ingredient of an analgesic Gewodin® being sold in Germany, is also metabolized into racemic MA to be excreted into urine. Nowadays, chiral analysis of amphetamines has become necessary, because of the above reasons.

For the final identification of a trace drug or poison in human specimens, the measurements of mass spectra are essential. Many methods for detection and determination of MA, AP and related compounds were reported using GC, HPLC, GC/MS and LC/MS. In this chapter, GC and HPLC are first presented as usual methods for analysis of MA, AP and related compounds; the methods by GC/MS and LC/MS are also described as the final confirmatory tests. In addition, a new capillary electrophoresis (CE) method for the compounds is also introduced.

Chemical structures of amphetamines and their related compounds to be dealt with in this chapter.

![Chemical structures](Figure 1.1)