— **Minireview** —

Characterization and Profiling of Methamphetamine Seizures

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Methamphetamine (MA) is the most common drug of abuse in Japan. MA is produced by chemical synthesis and final products of the drug contain small amounts of precursor chemicals, intermediates and by-products. Chirality is a principal characteristic of MA for evaluating the precursor chemicals. Adulterants such as dimethyl sulfone might be associated closely with trafficking routes of illicit drugs. Drug profiling is a scientific tool to identify the synthesis route, the sources of supply, trafficking routes and connections between seizures, which supports drug law enforcement agencies in their effort to eliminate organized drug crime. This review summarizes methods for characterization and profiling of MA hydrochloride, mainly based on our findings.

Key words —— methamphetamine, impurity profiling, gas chromatography, chirality, capillary electrophoresis

INTRODUCTION

Drug abuse is one of the most serious social problems throughout the world. There are many kinds of drugs of abuse, derived from either natural products or chemical synthesis. The former include opium, cocaine, cannabis and 'magic mushrooms,' and the latter include various excitatory amphetamines and hallucinogenic tryptamines. Heroin might be categorized into the intermediate class. This includes drugs that are produced by chemical synthesis from natural products, such as opium, which are themselves often abused in their natural state. Methamphetamine (MA) is the most common drug of abuse in Japan, and more than 80% of all reported violations of drug control laws are related to MA.[1] Street names for MA include shabu, speed, "S," and ice.

Most seized drugs contain impurities that originate from the manufacturing process, whether they are derived from natural plants or chemical synthesis. The amount of impurities varies widely, depending on the kind of drugs and the degree of purification. Every drug has its own characteristic impurities that carry information about the origin of the drug. These impurities can be used to identify the synthesis route and manufacturing methods, and to identify drug seizures of the same origin. In addition, seized drugs often contain adulterants (or diluents), which may be added at any stage in the distribution chain, subsequent to drug manufacture. These are also characteristic of individual drug seizures.

MA is produced by chemical synthesis, and the final product of the drug (crystals or powder) contains small amounts of precursor chemicals, intermediates and by-products. MA and its precursor chemicals ephedrine (EP) and pseudoephedrine (pEP) are chiral compounds, because of their asymmetric carbon atoms. Chirality of these compounds can be useful for estimating the precursor chemicals.

Drug profiling is a scientific tool to identify the synthesis route, sources of supply, trafficking routes and connections between seizures, which support drug law enforcement agencies in their efforts to eliminate organized drug crime. This review summarizes methods for characterization and profiling of MA hydrochloride (HCl) mainly based on our findings.

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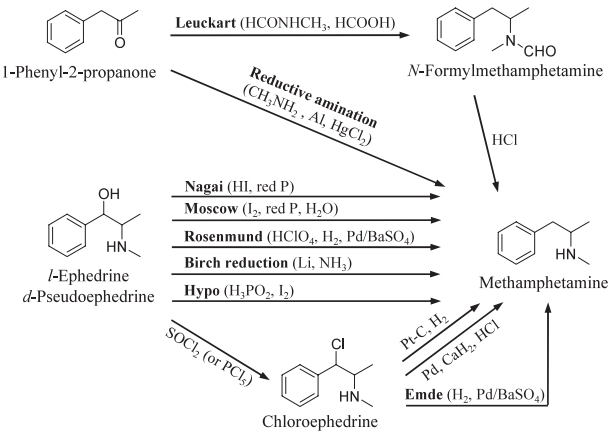

Fig. 1. Synthesis Routes of MA

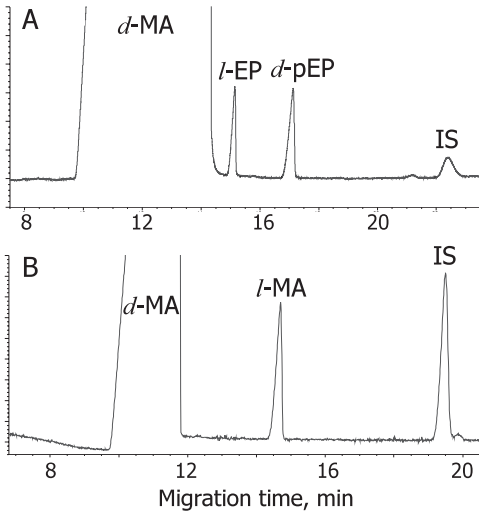

Fig. 2. Electropherograms of MA Seizures
EP, ephedrine; pEP, pseudoephedrine; IS, *d*-isoproterenol.

ROUTES OF MA SYNTHESIS

MA can be manufactured by a number of routes, as shown in Fig. 1. Two major synthetic groups can be distinguished: (a) synthesis starting from 1-phenyl-2-propanone (P2P), which yields racemic MA, such as the Leuckart method and reductive amination; and (b) synthesis using *l*-EP or *d*-pEP as starting materials, which yields *d*-MA that is more potent for the central nervous system than the racemic form. The latter routes include the Nagai, Moscow, Rosenmund, Birch reduction, Hypo,[2] and Emde methods, with chloroephedrine as an intermediate.

Most of the MA smuggled and abused in Japan is the *d*-form, which is manufactured from *l*-EP or *d*-pEP, whereas the racemic form or unequal proportions of *d*- and *l*-MA may be found in some cases.[3–5] Lee *et al.*[6] have reported that MA seizures that contain the *l*-form began to appear in 1997 in Korea, and rose continually to comprise up to 50% of seizures in 2005, which implies that the smuggling routes and/or precursor chemicals have changed recently.

PRECURSOR CHEMICALS IN MA HCl

Chiral information is essential for identifying the precursor chemicals, synthesis route, and intrinsic characteristics of MA seizures. We have investigated the simultaneous chiral separation of nine amphetamine-type stimulants by reversed-polarity capillary electrophoresis (CE) with a UV detector, using highly sulfated γ-cyclodextrin as a chiral selector.[7] CE was successfully connected with mass

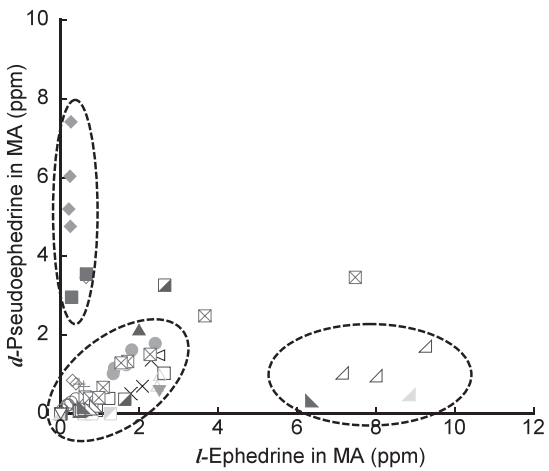

Fig. 3. Variability of *l*-EP and *d*-pEP Contents in MA Hydrochloride Crystals Seized in Japan
Data from 64 MA samples were plotted on the scatter diagram with different symbols. The same symbol indicates MA samples from the same seizure case. The seized samples were roughly classified into 3 groups shown in dotted circles. Redrawn from Iwata *et al.*[9]

spectrometry (MS), by modifying the run buffer for definite identification of the analytes.[8]

Reversed-polarity CE has been applied to the analysis of precursor chemicals in MA seizures.[9] Peaks derived from *l*-EP and *d*-pEP appeared beside a huge peak of *d*-MA on an electropherogram (Fig. 2A). In another case, a *d*-MA seizure had a small amount of *l*-MA (Fig. 2B), which suggests that the synthesis was performed via P2P routes, followed by incomplete chiral purification.

Content of *l*-EP and *d*-pEP in MA HCl crystals was determined quantitatively by CE (Fig. 3).

Based on the contents of two precursor chemicals, the seized samples were roughly classified into three groups. Thus, determination of chirality of MA provides useful information about the precursor chemicals, and content of *l*-EP and *d*-pEP is useful in grouping of MA seizures.

ADULTERANTS IN MA SEIZURES

MA that circulates illegally in Japan is generally in the form of white crystals, and its purity is mostly very high. However, in recent years, forensic science laboratories have experienced MA HCl seizures mixed with dimethyl sulfone (DMS), which is known as a common adulterant of the drug. Seizures of MA adulterated with DMS have also been reported in the U.S.A.,[10,11] Australia[12] and Korea.[13] Dimethylamphetamine HCl, EP HCl, sodium thiosulfate, sodium chloride, sodium glutamate and a mixture of caffeine and sodium benzoate are also known as adulterants of MA.

DMS is a highly polar compound that dissolves freely in water, methanol and acetone. It is used industrially as a high-temperature solvent for many inorganic and organic substances, such as a base material for cosmetics. No significant effects of DMS on the central nervous system have been reported. DMS is considered to be mixed with MA HCl crystals or powder solely to increase drug weight.

A simple method has been developed for simultaneous determination of MA and DMS in seized MA by fast gas chromatography (GC).[14] The use of a narrow-bore (0.1 mm internal diameter) capillary column gives fast and complete separation of three compounds including diphenylmethane as an internal standard (IS) within 1.3 min (Fig. 4). The method has been used to quantify MA and DMS in MA HCl crystals or powder samples recently seized in Japan. Out of 127 samples, 41 (32%) contained DMS, the contents of which were mostly less than 50%, although six samples contained more than 70% DMS. The research confirmed varying degrees of adulteration of recently seized MA HCl with DMS in Japan.

IMPURITY PROFILING

A variety of synthesis routes for MA have been previously described. Even if the same MA were obtained with the same synthesis route, impurities in MA HCl crystals would show variability because of differences in exact reaction conditions, as well as the purification and crystallization procedures, and the reagents and catalysts used in crude clandestine laboratories. The impurities are often present in very low concentrations, and chemical procedures are needed for their effective extraction. Usually chromatographic methods are used for the analysis of the extracted impurities. The majority of the methods utilize GC with either flame ionization detection (FID) or MS because of their high resolution, although high-performance liquid chromatography and capillary electrochromatography could be used for this purpose.[15] The resulting chromatograms are often referred to as profiles, and evaluation of similarities between different samples is performed by visually or statistically comparing the corresponding profiles.

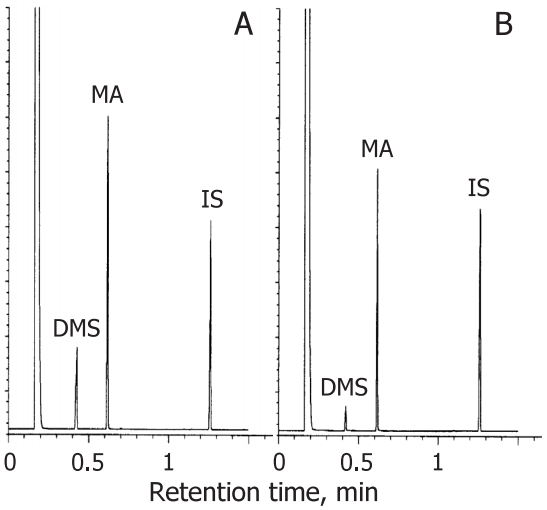

Fig. 4. Typical Gas Chromatograms Obtained from (A) the Authentic Standard Solution of MA and DMS and from (B) the Extract of a Seized Sample
IS, diphenylmethane. Redrawn from Inoue *et al.*[14]

GC Analysis

Sample pretreatment by liquid-liquid extraction (LLE) for MA impurity profiling has been known for more than 20 years. The procedure must be simple, robust and reproducible over a long time period. We have developed a method for impurity profiling of MA HCl with high purity.[16,17] In this method, MA impurities were extracted with ethyl acetate containing four ISs (*n*-decane, *n*-pentadecane, *n*-eicosane and *n*-octacosane) under alkaline conditions. GC-FID analysis was performed on a nonpolar capillary column (DB-5, 0.32 mm i.d. × 30 m,

1.0 μm film thickness). The use of the middle-bore column offered better separation of the impurity peaks without MA peak broadening (Fig. 5). Improved correction of retention times with four ISs permitted a satisfactory identification for a long time period, even when the column was replaced with a new one and when data were compared with different laboratories.[12, 13, 17–19)]

A similar extraction procedure, in which impurities were extracted with ethyl acetate under alkaline conditions, can be found in recent literature.[20–23)] A European research group reported a method for MA impurity profiling by GC-MS.[24)] In that method, impurities were extracted with toluene under weak alkaline conditions (pH 8.1).

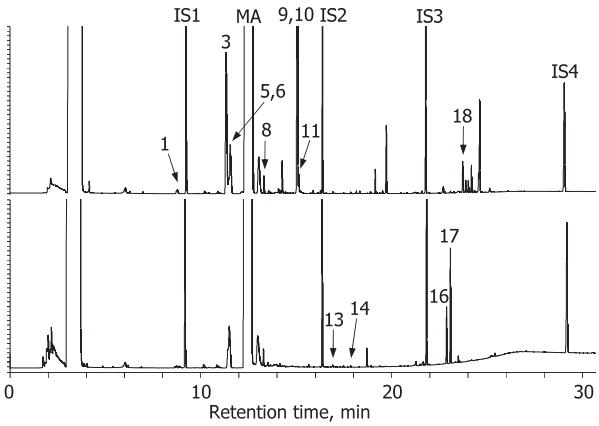

Fig. 5. Typical Gas Chromatograms of MA Impurity Profiling Using LLE of Samples

Names and chemical structures of impurity peaks were shown in Fig. 5. IS1, *n*-decane; IS2, *n*-pentadecane; IS3, *n*-eicosane; IS4, *n*-octacosane.

Identification of Impurities

Route-specific impurities or markers are the compounds that are only present in drugs synthesized via a certain route. *cis*- and *trans*-1,2-Dimethyl-3-phenylaziridines can be considered marker compounds, as their formation during MA synthesis is specifically related to EP/pEP (Fig. 6).[25)] A pair of two naphthalenes, 1,3-dimethyl-2-phenylnaphthalene and 1-benzyl-3-methylnaphthalene, are considered specific for the Nagai method (*l*-EP or *d*-pEP with hydriodic acid and red phosphorus). P2P is known as the precursor chemical for Leuckart reaction and reductive amination routes whereas it is also a by-product of EP routes.

Evaluation of Similarity

There are several statistical indices for computerized comparison of chromatograms. Euclidean distance, cosine distance and correlation coefficient are defined as following equations.

$$\text{Euclidean distance} = \left[\sum (X_{ik} - X_{jk})^2\right]^{1/2}$$

$$\text{cosine distance} = \frac{\sum \left(X_{ik} \cdot X_{jk}\right)}{\left[\sum X_{ik}^2 \cdot \sum X_{jk}^2\right]^{1/2}}$$

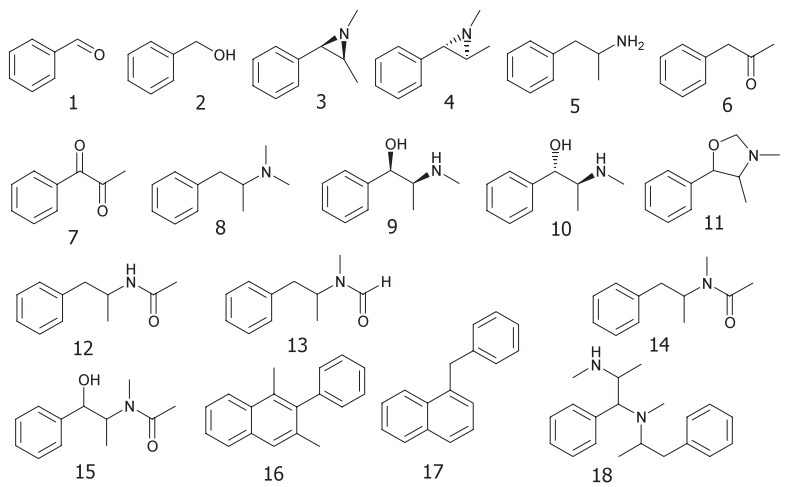

Fig. 6. Chemical Structures of Impurities in MA

1, benzaldehyde; 2, benzylalcohol; 3, *cis*-1,2-dimethyl-3-phenylaziridine; 4, *trans*-1,2-dimethyl-3-phenylaziridine; 5, amphetamine; 6, 1-phenyl-2-propanone; 7, 1-phenyl-1,2-propanedione; 8, *N*,*N*-dimethylamphetamine; 9, EP; 10, pEP; 11, 3,4-dimethyl-5-phenyloxazolidine; 12, *N*-acetylamphetamine; 13, *N*-formylmethamphetamine; 14, *N*-acetylmethamphetamine; 15, *N*-acetylephedrine; 16, 1,3-dimethyl-2-phenylnaphthalene; 17, 1-benzyl-3-methylnaphthalene; 18, MA-dimmer.

$$\text{correlation coefficient} = \frac{\sum (X_{ik} - X_i) \cdot \left(X_{jk} - X_j\right)}{\left[\sum (X_{ik} - X_i)^2 \cdot \sum \left(X_{jk} - X_j\right)^2\right]^{1/2}}$$

X_{ik} and X_i represent area of peak k in sample i and the averaged area of the selected peaks of sample i, respectively.

Other indices such as Manhattan distance, Canberra distance, similarity index, squared sine and Quotient method, could be found in the literature on amphetamine profiling.[26] The most commonly known index is probably the Euclidean distance. When MA HCl crystals were diluted with adulterants in varying degrees, profiling analysis would show chromatograms with different areas of impurity peaks, but the same proportions. In these cases, the use of cosine distance and/or correlation coefficient would be effective for comparative analysis.

We usually evaluate similarity and/or dissimilarity of the chromatographic profiles between samples by using the Euclidean distances of selected impurity peak areas after common-logarithmic transformation.[17] Figure 7 shows a dendrogram obtained from a hierarchical cluster analysis of MA crystals seized in Japan and Thailand. MA samples were classified roughly into four groups based on the characteristics of their impurities. The use of the same profiling method facilitates direct comparison and data sharing of MA profiles internationally.

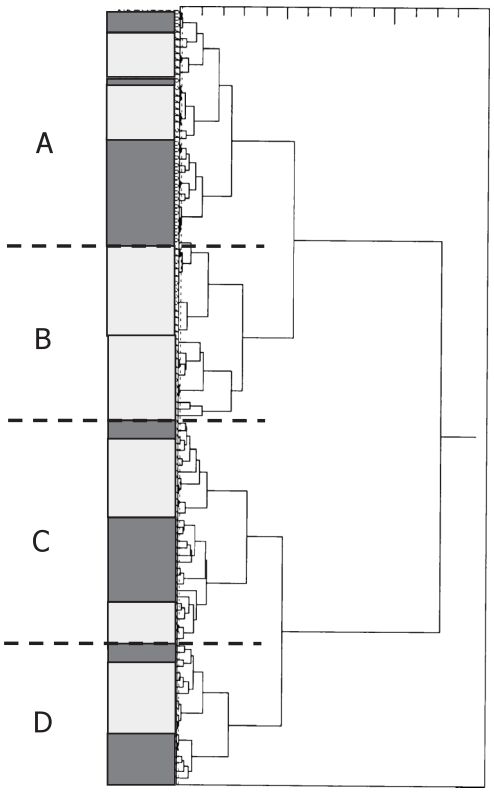

Fig. 7. Dendrogram Obtained from a Cluster Analysis of MA Crystals Seized in Japan and Thailand

Sixty-nine samples seized in Japan and 42 samples in Thailand were classified into four groups (A to D). Open and solid bars represent clusters formed by samples in Japan and in Thailand, respectively. The numbers of samples (Japan/Thailand) classified into each group are 15/19 for A, 25/0 for B, 17/15 for C and 12/8 for D. Redrawn from Kuwayama *et al.*[17]

Alternative Sample Pretreatment

Headspace solid phase microextraction (HS-SPME) is a technique often used for the analysis of volatile compounds in air, beverages, water, etc. Methods using HS-SPME for the characterization of MA[11,27] and 4-methoxyamphetamine[28] have been reported. HS-SPME is simple, rapid and solvent-free, because it is based on the partitioning of analytes between a fiber coated with stationary phase and the sample matrix, and would provide additional information in terms of characterizing MA samples.

We have investigated the applicability of HS-SPME coupled with GC-MS for impurity profiling of MA HCl.[29] The relative intensity of impurities in MA determined by HS-SPME was much greater than that by LLE. HS-SPME enabled the effective extraction of impurities without an overload of MA to GC-MS (Fig. 8). Furthermore, trace amounts of ethanol, diethyl ether and acetic acid, which were considered to be reagents and solvents used during MA synthesis, were also detected on some of the chromatograms. The method would be useful and effective for the impurity profiling of MA, and would also provide supplementary information

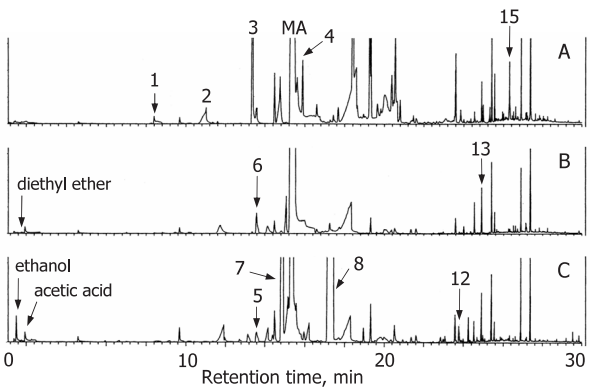

Fig. 8. Total Ion Current Chromatograms of MA Impurity Profiling Using HS-SPME of Samples

Names and chemical structures of impurity peaks were shown in Fig. 5. Redrawn from Kuwayama *et al.*[29]

relative to results obtained by a conventional LLE method.

Like HS-SPME, thermal desorption (TD) is also a simple, rapid, and solvent-free extraction method. Because a TD instrument enables the direct introduction of a sample without any laborious extraction procedure, it is effective for analyzing trace amounts of compounds, particularly volatiles. TD/GC-MS was applied to impurity profiling of MA in an attempt to develop a method that simplifies preparation and enables the detection of specific volatile compounds.[30] Impurity profiling of MA using TD and HS-SPME was compared with that using LLE. Better reproducibility of peak areas was obtained using LLE, whereas higher intensities and numbers of peaks were detected using TD and HS-SPME. Solvents were extracted more effectively using TD. TD, as well as HS-SPME, can be used to provide supplemental information for LLE, and the combination of these extraction methods can be effective for comprehensive impurity profiling of MA.

ANOTHER APPROACH

Many elements exist as different isotopes. Isotopes of the same element share very similar chemical properties, but their physical properties differ slightly. The composition of isotopes, which can be used for classification and differentiation of illicit drugs,[31–34] may vary depending on the origin of the precursor chemicals or the drug itself. Determination of stable isotope ratios of nitrogen and carbon of MA could provide valuable information for profiling of MA seizures from another aspect.[35, 36]

CONCLUSION

Methods for characterization and profiling of MA seizures were outlined. Chirality is a principal characteristic of MA to evaluate the precursor chemicals. Even if the purity of MA HCl seizures was higher than 99%, trace levels of impurities could exist in the crystals or powders. Impurity profiling could provide us useful information regarding synthesis routes and connections between MA seizures. Adulterants such as DMS might be associated closely with trafficking routes of illicit drugs.

Combination of advanced technologies for characterization of MA seizures could provide useful information regarding the synthesis route, sources of supply, trafficking routes, and connections between seizures, supporting the efforts of drug law enforcement to eliminate organized drug crime.

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