Case report

Monitoring precursor chemicals of methamphetamine through enantiomer profiling

Jae Sin Lee a,b, Wun Kyung Yang a, Eun Young Han a, Soo Yeun Lee a, Yong Hoon Park a, Mi Ae Lim a, Hee Sun Chung a, Jeong Hill Park b,*

a National Institute of Scientific Investigation, Department of Narcotics Division, Seoul 158-707, Republic of Korea
b Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul 151-742, Republic of Korea

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Abstract

Smuggling of methamphetamine is affected by enforced regulation and international situation, resulting in changes of precursors and synthetic methods used. Enantiomer ratio of methamphetamine can provide information concerning its precursor and synthetic method. This information is useful for the prevention of smuggling methamphetamine and its precursor, and resultant reduction of methamphetamine abuse. In the present study, we investigated on the enantiomer ratios of 433 crystalline methamphetamine samples seized in Korea from 1994 to 2005. Excluding 17 samples of low purity, 416 samples were used for enantiomer profiling. The methamphetamine samples were derivatized with (S)-( +)-a-methoxy-a-(trifluoromethyl)phenylacetyl chloride ((S)-( +)-MTPACl), and the derivatives were analyzed by GCMS in selected ion monitoring (SIM) mode. The enantiomer ratios of the samples were calculated from the standard calibration curves of each enantiomer, both of which showed good linearity in the range of 0–1.2 μg. Most of the seizures were pure (S)-( +)-enantiomer, but 21% (95 of 416 samples) contained (R)-( -)-enantiomer above 1%. They began to appear from 1997, and increased continuously up to 50% in the year 2005 (55 of 111 samples). From this study, we could find out that alternative precursors have been used recently for the illicit manufacture of methamphetamine seized in Korea.

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1. Introduction

Abuse of amphetamines (ATS) has increased continuously throughout all over the world, and has become a global problem in recent years. Cunningham and Liu [1] have reported that the precursor regulations in the United States had an impact on reducing the number of arrests and hospital admissions. However, the number of arrests rebounded fully within 2–3 years, as original precursors have changed to new ones. The clandestine manufacturers tend to move from one area to another in order to escape from regulations. It has been reported that pure preparations of methamphetamine had been manufactured in South Korea and Taiwan until the 1980s [2], but “technology transfer” has occurred as a result of enforced regulation. Most of the clandestine laboratories have disappeared in South Korea, and illicit methamphetamine is manufactured and smuggled mainly from foreign sources at present.

Methamphetamine has an asymmetric center at C-2, and there are two enantiomers, S( +)- and R( -)-methamphetamine. Psychostimulant effects of amphetamines are enantioselective, and S( +)-enantiomer is about five times as active as R( -)-enantiomer [2]. For its high stimulant effect, S( +)-enantiomer is predominately abused and illicitly smuggled in the black markets. On the other hand, R( -)-enantiomer has been used as a decongestant in nasal inhalers in the United States, and it can also be used as a precursor for the manufacturing of l-deprenyl, an effective antiparkinsonian and antidepressant [3]. Enantiomeric property of methamphetamine sample is determined by enantiomeric configuration of the precursors (Fig. 1). 1R,2S( -)-ephedrine, 1S,2S( +)-pseudoephedrine and their derivatives have the same C-2 configuration with S( +)-methamphetamine, so they can be used as a precursor of S( +)-methamphetamine. They are often extracted from Ephedra plant (“Ma Huang”) and used for the clandestine synthesis of methamphetamine [4,5]. On the contrary, R( -)-methamphetamine can be synthesized from 1R,2R( -)-pseudoephedrine, 1S,2R( +)-ephedrine and their derivatives.

* Corresponding author. Tel.: +82 2 880 7857; fax: +82 2 874 8928.
E-mail address: hillpark@snu.ac.kr (J.H. Park).

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methamphetamine can be produced from benzylmethylketone (BMK) by reductive amination or Leuckart reaction. Enantiomer ratio of methamphetamine is closely related with the species of precursors and reagents used for the synthesis, and it can provide useful information concerning the origins and synthetic methods used for illicit manufacture. This information is important, since it can be utilized for regulation of the precursors, investigation of the manufacturing sources, and resultant prevention of abuse. In this work, we investigated on the trend of precursors through the enantiomer analysis of methamphetamine seized in Korea from 1994 to 2005.

Usually, enantiomer ratio of methamphetamine is measured through capillary electrophoresis (CE) [6–8], HPLC [9–12] and GC–MS [13–20]. Among the analytical techniques, GC–MS has been widely used for its convenience. Methamphetamine should be converted to diastereomers with chiral-derivatization reagents to be resolved by gas chromatography with nonchiral column. N-(trifluoroacetyl)prolyl chloride (TPC) [13–16], α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) [17,18], α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) [19,20] and heptafluorobutylprolyl chloride (HFBPCl) [21] are generally used for the chiral-derivatization of methamphetamine. Among the reagents, TPC has been widely used for the analysis of methamphetamine enantiomers, and it was used in our laboratory in the previous study [13]. However, TPC contains enantiomeric impurity originated from reagent, and it causes false-positive result [13,17]. On the contrary, MTPA derivative is free of enantiomeric impurity, so we used (S)-(+)–MTPACl as a chiral-derivatization reagent in this study.

2. Experimental

2.1. Materials

We used 433 methamphetamine samples, which were seized in Korea from 1994 to 2005 by the National Police Agency and the Prosecutor’s Office. The standards of S(+), R(−), (±)-methamphetamine, and (±)-methamphetamine–d₄ were purchased from Cerilliant (Round Rock, Texas, USA). (S)(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride ((S)(+)-MTPACl) of 99% purity was obtained from Aldrich (St. Louis, MO, USA).

2.2. GC–MS parameters

GC–MS analysis was carried out on a Hewlett-Packard HP5973 mass selective detector (MSD) equipped with HP6890 gas chromatography, HP7683 automatic sampler, and HP-5MS capillary column (30 m × 0.25 mm × 0.25 μm film thickness) (Agilent Technologies Co., USA). Helium was used as a carrier gas and the flow rate was 1 ml/min. Injector temperature was set at 250 °C, and temperatures of interface and MS ion source were set at 285 °C and 230 °C, respectively. Oven temperature was programmed as follows; an initial temperature was 140 °C and held for 0.5 min, followed by an increase of 35 °C/min to 215 °C and held for 1.5 min, and then 10 °C/min to 285 °C and held for 5 min. Mass spectral data was acquired in selected ion monitoring (SIM) mode. The ions selected for methamphetamine and its deuterated internal standard were m/z 274 and 278, respectively.

2.3. Standard and sample preparation

We used 0, 40, 80, 120, 160, 200, and 240 μl of (±)-methamphetamine standard solutions (10 μg/ml in ethanol) for calibration, which contained 0–1.2 μg/ml of both enantiomers. Each seized sample was diluted to 10 μg/ml with ethanol, and 100 μl was used for analysis. Each standard and sample solution was transferred to each test tube, and 200 μl of (±)-methamphetamine–d₄ (10 μg/ml in ethanol) was added as internal standard. After evaporation using nitrogen stream, 40 μl of (S)(+)-MTPACl solution (50 mg/ml in dry CH₃CN) was added to the test tube, and the standard and sample solutions were derivatized at 70 °C for 1 h. Then they were cooled to room temperature, and excessive derivatization reagent was converted to ethyl ether by adding 100 μl of anhydrous ethanol and heating them at 70 °C for 15 min [17]. After evaporation, the residue was dissolved in 100 μl of ethyl acetate, and 2 μl was injected to GC–MS. Derivatization and injection of a sample were replicated three times in cases R(−)-enantiomer was detected, and the mean value of the replications was adopted finally.

2.4. Calculation of LOD and R(−)-enantiomer ratio

Limit of detection (LOD) of each enantiomer was calculated from the calibration curves of 0, 20, 40, 80, 200, 320, and 400 μl of (±)-methamphetamine standard solutions (0.5 μg/ml in ethanol), which contained 0–0.1 μg of

Fig. 1. Enantiomers of methamphetamine originated from different precursors. EP, ephedrine; PE, pseudoephedrine; MA, methamphetamine; P2P, 1-phenyl-2-propanone.
both enantiomers. Each standard was derivatized and analyzed by the same way described above, and the LODs were calculated following the definition below [22].

Limit of detection (LOD) = \( y_B + 3s_B \)

where \( y_B \) and \( s_B \) represent blank signal and standard deviations of the blank, respectively.

Enantiomer ratio of \((\pm)\)-methamphetamine standard, analyzed by direct comparison with unalloyed \(S^+\) and \(R^-\)-methamphetamine, was 50:50. Peak area ratios of the standards to its deuterated internal standards were used to get calibration curves. Content of each enantiomer in a sample was calculated from each calibration curve, and \(R^-\)-enantiomer ratio of a sample was calculated as percentage of \(R^-\) to total enantiomer.

3. Results and discussion

Selected ions of \(m/z\) 274 and 278 were specific for methamphetamine and its deuterated internal standard. There was no interference between them, and we could obtain baseline-resolved result in this work (Fig. 2). Standard calibration curves of \(S^+\) and \(R^-\)-enantiomer showed good linearity in the range of 0–1.2 \(\mu\)g \((R^2 > 0.999)\), and the LODs were 0.002 \(\mu\)g for both enantiomers. Purity of most samples was above 70% except 17 samples, that of which ranged between 4 and 63%. Three samples among seizures in 2000, 2001 and 2005 were insufficiently purified, and two samples of 2004 contained large amount of dimethylamphetatine, an impurity originated from methylephedrine. One sample of 1996 was adulterated with dimethylsulfone, and the other 11 samples seized between 1999 and 2005 were diluted with alum. Appearance of methamphetamine diluted with alum suggested deficiency in supply of methamphetamine. Purity was over 70% in 416 samples, and they were used for the enantiomer profiling in this study.

Differences in enantiomer ratios imply that the methamphetamine samples were synthesized from different precursors by different methods. Methamphetamine samples were classified to four groups according to their enantiomer ratios. Their pattern is presented in Table 1, and typical SIM chromatograms of the samples representing the four groups are shown in Fig. 3. The \(S^+\)-enantiomer eluted before the \(R^-\)-enantiomer, and their deuterated internal standards appeared just prior to each enantiomer.

Out of 416 samples, 321 samples were optically pure \(S^+\)-enantiomer containing \(R^-\)-enantiomer below 1%. \(R^-\)-enantiomer was detected above 1% in 95 samples. Among the 95 samples, 48 samples contained 1–20% \(R^-\)-enantiomer, 21 samples 20–80%, and 26 samples above 80%. Among the 26 samples, 17 samples even contained \(R^-\)-enantiomer over 99%.

All of the methamphetamine samples seized from 1994 to 1996 were optically pure \(S^+\)-enantiomer. Seized samples containing enantiomeric impurity began to appear from 1997, and racemic mixture and even \(R^-\)-enantiomer began to appear from 1999 and 2001. Methamphetamine containing \(R^-\)-enantiomer above 1% have gradually increased since 1997, and rapidly in 2003.

This result implied that it was relatively easy to obtain optically pure ephedrine compound until 1996, but clandestine manufacturers got to have difficulties in obtaining it since 1997. It may have been resulted from the regulation on ephedrine compounds used for the manufacture of illicit methamphetamine, and the regulation may have enforced clandestine manufacturers to use alternative precursors. Moreover, significant rise in 2003 may have been influenced mainly by the regulation enforced by the Korean government in 2002 and by the sea blockade enforced during 2002–2003 in the open sea around Korea. The domestic and international factors have

**Table 1**

<table>
<thead>
<tr>
<th>(R^-)-ratio</th>
<th>Seized year</th>
</tr>
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<tbody>
<tr>
<td>&gt;80%</td>
<td>1</td>
</tr>
<tr>
<td>20–80%</td>
<td>1</td>
</tr>
<tr>
<td>1–20%</td>
<td>1</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
</tr>
</tbody>
</table>

Samples used are a part of total seizures in Korea, and the sample numbers do not correspond with the number of total seizures. "\(R^-\)-ratio" is the abbreviation of the \(R^-\)-enantiomer ratio.
affected the smuggling of methamphetamine and/or its precursor, resulting in the changes of smuggling routes and sources. Methamphetamine containing \( R(-) \)-enantiomer rose continuously up to 50\% in the year 2005 (55 of 111 samples), which shows that smuggling routes and/or precursors have changed recently.

Makino et al. [23] have reported that \( 1R,2S(-) \)-ephedrine and \( 1S,2S(+)- \)pseudoephedrine were identified in the illicitly manufactured \( S(+) \)-methamphetamine, but ephedrine compounds were not identified in \( R(-) \)- or racemic methamphetamine. General characteristics of \( R(-) \)- or the mixture of \( R(-) \)- and \( S(+) \)-methamphetamine samples are high purity with few impurities and no or trace amount of ephedrine compounds. Instead, methylephedrine, methylpseudoephedrine, P2P and benzylcyanide were identified, and they may have been used as precursors of the seized methamphetamine samples.

Ephedrine has been reported as the major precursor of methamphetamine seized in Korea until 1980s [24]. Ephedrine compounds may still be used as a precursor of methamphetamine in general, but less than previous. Most of the \( R(-) \)- or the mixture of \( S(+) \)- and \( R(-) \)-enantiomers may have been prepared from other chemicals of legal drugs than ephedrine compounds. \( R(-) \)-methamphetamine may be related with chiral precursors such as \( 1S,2R(+)- \)methylpseudophedrine or \( 1R,2R(-) \)-methylpseudoephedrine. Mixture of \( S(+) \)- and \( R(-) \)-methamphetamine may have been synthesized from enantiomeric mixtures such as racemic methylpseudophedrine, or other achiral precursors such as P2P or benzylcyanide.

Iwata et al. [6] have reported that the methamphetamine samples seized recently in Japan and in the United States contained \( R(-) \)- or the mixture of \( S(+) \)- and \( R(-) \)-enantiomers as well as \( S(+) \)-enantiomer. Smuggling of the methamphetamine between these countries may be related with each other, and some of the methamphetamine samples seized in these areas may have the same origin. Monitoring of enantiomer ratio will help to understand the smuggling pattern of methamphetamine between the related countries, and it will support to prevent the smuggling of methamphetamine and precursor chemicals.

4. Conclusion

Due to the increase of methamphetamine containing \( R(-) \)-enantiomer, enantiomer ratio has become another factor to be considered for the profiling of methamphetamine. Enantiomer ratio will serve as useful information for the regulation of precursor chemicals, and will consequently reduce clandestine manufacture of methamphetamine and its abuse. Methamphetamine containing above 1\% of \( R(-) \)-enantiomer has appeared since 1997, significantly increased in 2003, and rose dramatically up to 50\% in the year 2005 (55 of 111 samples). It indicates that precursor regulation has taken effect since 1997, and precursor chemicals and/or smuggling routes changed comparatively in 2003. As a result of the precursor regulation, clandestine laboratories may have difficulties in obtaining optically pure ephedrine compounds. From this study, we could conclude that alternative precursors have gradually increased since 1997, and grew significantly in 2003.

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References


