Methiopropamine

Critical Review Report

Agenda item 4.23

Expert Committee on Drug Dependence

Thirty-sixth Meeting

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Acknowledgements

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD:
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Summary

Methiopropamine was first synthesized in 1942 but has recently appeared on drug websites offering “legal highs” as an attempt to circumvent laws controlling amphetamines [1]. Methiopropamine is a methamphetamine analogue in which the benzene ring has been exchanged with a thiophene ring and is described to have similar effects. Adverse effects reported from internet forums are chest tightening, increased sweating and increased heart rate.

There are currently no studies available on the toxicity and abuse of methiopropamine either in animals or in humans. Only a few cases of intoxication due to methiopropamine ingestion have been reported.
1. Substance Identification

   A. International Non-proprietary Name (INN)
      \(N\)-methyl-1-(thiophen-2-yl)propan-2-amine

   B. Chemical Abstract Service (CAS) Registry Number
      801156-47-8 free base
      7464-94-0 hydrochloride salt

   C. Other chemical names
      MPA
      Methiopropamine
      \(N,\alpha\)-dimethyl-2-thiopheneethanamine
      \(N\)-methyl-1-(thiophen-2-yl)propan-2-amine

   D. Trade names
      “Slush Eric”, MPA

   E. Street names
      “Blow”

   F. Physical properties
      The hydrochloride salt of methiopropamine is a crystalline powder at room temperature.

   G. WHO Review History
      Methiopropamine was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO’s attention that methiopropamine is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

   A. Chemical Name
      IUPAC Name: 1-(thiophen-2-yl)-2-methylaminopropane
B. Chemical Structure

Free base:

![Chemical Structure](image)

Molecular Formula: C₈H₁₃NS
Molecular Weight: 155.26 g/mol
Melting point: 84.308 °C
Boiling Point: 215.8 ± 15.0°C at 760 mm Hg

C. Stereoisomer

Two enantiomers, the chiral center is marked with a star below.

![Stereoisomer](image)

D. Synthesis

There is a four step synthesis of methiopropamine. It begins with (thiophen-2-y1) magnesium bromide, which is reacted with propylene oxide, yielding 1-(thiophen-2-yl)-2-hydroxypropane which is reacted with phosphorous tribromide, yielding 1-(thiophen-2-yl)-2-bromopropane which is finally reacted with methylamine, yielding 1-(thiophen-2-yl)-2-methylaminopropane [2].

E. Chemical description

Methiopropamine is a structural analogue of methamphetamine in which the phenyl group has been replaced with thiophene ring.

F. Chemical properties

Methiopropamine hydrochloride (salt) is soluble in organic solvents like ethanol (20 mg/mL), DMSO (10 mg/mL) and dimethyl formamide (20 mg/mL) and in aqueous, nonorganic solvents like PBS (2 mg/mL).

G. Chemical identification

Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) have been used for identification of methiopropamine [3-5]. IR spectroscopy, gas chromatography-mass spectrometry (GC-MS) and proton/carbon NMR spectroscopy have been used to identify methiopropamine [6].
3. Convertibility into controlled substances

Methiopropamine is not readily converted into other controlled substances.

4. General Pharmacology

Methiopropamine, a structural analogue of methamphetamine, functions primary as a norepinephrine-dopamine reuptake inhibitor and, secondary, as a serotonin reuptake inhibitor. These interactions have been determined by in vitro studies [7].

4.1. Pharmacodynamics

At present, very little is known due to the lack of information on methiopropamine in the scientific literature. Methiopropamine displays similar properties as methamphetamine including stimulation, alertness and increase of focus and energy. Side-effects following administration that have been reported is tachycardia, anxiety, panic attacks, perspiration, headache, nausea, difficulty in breathing, vomiting, difficulty urinating and sexual dysfunction [8, 9].

4.2. Routes of administration and dosage

Methiopropamine is generally administrated by insufflation, inhalation or orally. The dosage is ranging from 5–60 mg insufflated, 5–40 mg by inhalation and 10–50 mg when taken orally. The onset of effects is revealed 5-10 min following administration. Rectal administration has also been reported in a few cases [10].

4.3 Pharmacokinetics

The duration of effect of methiopropamine is suggested to be 2-4 hours following insufflation. However, effects may occur up to 24 hours following administration. Inhalation of vaporized methiopropamine displays the plateau at 1-2 hours [8].

The main metabolite detected in urine in the N-demethylated metabolite nor-MPA, showing that methiopropamine is only metabolized to a minor extent. The metabolism includes the cytochrome P450 enzyme CYP2C19 in the liver. In in vitro studies, traces of methiopropamine hydroxy metabolites could also be detected. However, these metabolites could not be identified in human urine [11-14].

5. Toxicology

Toxicity in Animals
No studies were identified that have examined the toxicity of methiopropamine in animals.
Toxicity in Humans
No studies were identified that have examined the toxicity of methiopropamine in humans.

6. Adverse reactions in humans

Cases of Methiopropamine Intoxication in Humans

Non-fatal Cases
In Sweden during 2013, 21 cases of methiopropamine intoxication were reported. The substance was detected in 15 cases in urine and 5 cases in blood [15].

Fatal Cases
Two fatal cases involving methiopropamine occurred in January 2012 in the U.K. detected in post-mortem sample analyses. Both cases involved other substances such as methoxetamine, MDAI and lignocaine [16].

In Sweden, one fatal case has been reported. The concentration of methiopropamine was determined to 1.3µg/g in femoral blood [16].

7. Dependence potential

No studies were identified that have examined the dependence potential of methiopropamine in animals or in human.

8. Abuse potential

No studies were identified that have examined the abuse potential of methiopropamine in animals or in human.

9. Therapeutic applications, extent of therapeutic use and epidemiology of medical use

No evidence has been found that methiopropamine has been therapeutically used.

10. Listing on the WHO Model List of Essential Medicines

Methiopropamine is not found on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

None known.
12. Industrial use

No evidence has been found that methiopropamine has been therapeutically used.

13. Non-medical use, abuse, dependence

Two cases of deaths have been reported in 2012, where methiopropamine was involved in combination with other drugs, e.g. methoxetamine, MDAI and lignocaine. Several hospital admissions both in Europe and in the US have been reported with symptoms which including anxiety, paranoia and vomiting.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

The global emergence of NPS reported in December 2013 the following countries highlighted methiopropamine: Australia, Netherlands, Canada, Norway, Estonia, Russian Federation, Finland, Singapore, Germany and the United Kingdom.


15. Licit production, consumption and international trade

Not applicable. Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit manufacture and traffic and related information

Reports of seizures of methiopropamine have been noticed in North America and Europe, especially in Canada and the UK. The amount is typically in milligram-gram amounts in powder form. The distribution and trafficking mainly occurs through the Internet. No specific reports on the licit and illicit production are available.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

Methiopropamine is not controlled under the United Nations conventions.
18. **Current and past national controls**

Methiopropamine is a controlled substance in the US state Florida and in Germany.

In the United States in general, methiopropamine is not controlled under the Controlled Substances Act (CSA). However, may be considered as a controlled substance analogue of methamphetamine.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. **Other medical and scientific matters relevant for a recommendation on scheduling of the substance**
References


15. Case collected from the Public Health Agency of Sweden, 2014

16. Information gathered from ROAR Forensics, UK, 2012
Annex 1:
Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of methiopropamine

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 63 Member States answered the questionnaire for methiopropamine (MPA). Of these, only 24 respondents (AMR 5, EUR 16, WPR 3) had information on this substance.

LEGITIMATE USE

None reported that MPA was currently authorized or in the process of being authorized/registered as a medical product in their country. Four respondents stated that this substance was used in research or as analytical reference standards. One respondent stated that there was use for MPA in veterinary care.

HARMFUL USE

Thirteen respondents confirmed that there was recreational/harmful use of MPA; the common route of administration was stated as oral by 5, oral/inhaling/sniffing by 2 and oral/injection/inhaling/sniffing by one. Seven respondents stated this was obtained via trafficking and one each clandestine manufacturing and diversion plus trafficking. Eleven respondents reported on the common formulations of MPA available with 5 reporting powder, 4 reporting powder and tablet, and one each liquid, and powder, tablet, liquid forms. When asked if MPA was used by any special populations 3 respondents stated that it was only used by the general population and 1 only in clubs. Two emergency room visits are reported for 2012. The same respondent reports seven emergency room visits and one death related to MPA (concentration 1,3 µg, flubromazepam was also found) in 2013. Two respondents reported yes to the question on withdrawal, tolerance and other adverse effects or medical illnesses caused by MPA.

CONTROL

Of those with information on this substance, 14 reported that MPA was controlled under legislation that was intended to regulate its availability; 8 under “controlled substance act”, 4 under “medicines law”, 1 under “analogue legislation” and 1 under “other” laws. Only 3 respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving MPA, one respondent reported clandestine manufacture. Three respondents reported processing into the consumer product, eight reported trafficking, two reported diversion and nine an internet market.
Details on seizures are presented below.

<table>
<thead>
<tr>
<th></th>
<th>2011 (number of respondents)</th>
<th>2012 (number of respondents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of seizures</td>
<td>12 (4)</td>
<td>234 (7)</td>
</tr>
<tr>
<td>Total quantity seized (kg)</td>
<td>0.01 (1)</td>
<td>0.89 (3)</td>
</tr>
<tr>
<td>Total quantity seized (tablets/pills)</td>
<td></td>
<td>518 (4)</td>
</tr>
</tbody>
</table>

**IMPACT OF SCHEDULING**

Twenty-one respondents reported that if MPA was placed under international control, they would have the laboratory capacity to identify the substance. There is no medical use reported.