1-(4-methoxyphenyl) piperazine (MeOPP)

Pre-Review Report

Expert Committee on Drug Dependence

Thirty-fifth Meeting

Hammamet, Tunisia, 4-8 June 2012

Acknowledgements

This report has been drafted under the responsibility of the WHO Secretariat, Essential Medicines and Health Products, Medicines Access and Rational Use Unit. The WHO Secretariat would like to thank the following people for their contribution in producing this pre-review report: Dr Simon Elliott, United Kingdom (literature review and drafting), Dr Caroline Bodenschatz (editing) and Mr Kamber Celebi, France (questionnaire report).

Contents

Summary

Although there is very little information available, 1-(4-methoxyphenyl)piperazine (MeOPP) is a piperazine derivative that appears to have mild stimulant (including euphoria) effects and some hallucinogenic properties. MeOPP has never been licensed as a medicine. Use has been noted from anecdotal reports in 2000 (e.g. USA) but the first report of seized material containing MeOPP appeared in 2006 in the UK. The mode of abuse is similar to that of "Ecstasy" with many users seeking MDMA-like effects, particularly with concomitant BZP, TFMPP or mCPP use. Many suppliers market the substance as "legal Ecstasy" or as a "legal high". Such products typically contain other piperazine derivatives in variable quantities. There are no published non-fatal or fatal hospital admissions. No specific studies have been performed to determine the abuse or dependence potential.

Pre-review of 1-(4-methoxyphenyl)piperazine (MeOPP)

1. Substance identification

A. International Nonproprietary Name (INN:

Not applicable

B. Chemical Abstract Service (CAS) Registry Number

38212-30-5 (free base)

C. Other Names

1-(4-methoxyphenyl)piperazine, 4-MeOPP, Methoxyphenylpiperazine *p*-methoxyphenylpiperazine, pMeOPP, 1-(4-Anisyl)piperazine. In Japan, it is called "4MPP"(Annex 1).

D. Trade Names

None.

E. Street names

MeOPP is not known to be associated with any particular street names but is present in branded pill products sold as a perceived legal “Ecstasy” alternative (e.g. “PEP” and “Twisted”).

One should be aware of the fact that street names are not always exclusive for just one substance

F. Physical properties

No data.

G. WHO Review History

Several reports suggest misuse of MeOPP over the last years. At the time being, neither BZP nor any other substituted piperazine is listed in the Schedules of the United Nations 1971 Convention on Psychotropic Substances. In order to bring more conclusive scientific evidence on the overall risks of MeOPP for an eventual international scheduling, the WHO Secretariat has decided to initiate at the 35th ECDD a pre-review.

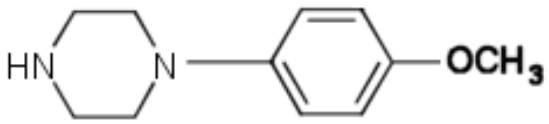
2. Chemistry

A. Chemical Name

IUPAC Name: 1-(4-methoxyphenyl)piperazine
CA Index Name: 1-(4-methoxyphenyl)piperazine

B. Chemical Structure

Free base:



Molecular Formula:	$C_{11}H_{16}N_2O$
Molecular Weight:	192.26 g/mol (free base)
Melting point:	42-47 °C
Boiling point:	n/a
Fusion point:	n/a

C. Stereoisomers

pMeOPP has no chiral centres and therefore no stereoisomers. Positional isomers of the methoxy moiety such as 2-MeOPP (oMeOPP) exist and are available but abuse is attributed to solely 4-MeOPP (pMeOPP), this is based on its presence in seized items but analytical confirmation may be difficult.

D. Synthesis

MeOPP is an entirely synthetic compound and is available from retail chemical suppliers. Synthesis information is not available.

E. Chemical description

No data.

F. Chemical properties

No data.

G. Chemical identification

Methods for the identification of MeOPP have been provided by Peters et al., (2003), Staack and Maurer (2003), Wohlfarth et al. (2010) and Moreno et al. (2012). For LC-MS or GC-MS, without sufficient chromatographic separation it would be difficult to determine the exact isomer present (i.e. oMeOPP or pMeOPP).

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

4.1. Pharmacodynamics

Neuropharmacology and effects on central nervous system:
Although some studies have been performed involving 1-(2-methoxyphenylpiperazine) (Minard *et al.*, 1979), only one publication involves 1-(4-methoxyphenylpiperazine) (Nagai *et al.*, 2007). Nagai *et al.* reported that MeOPP inhibited monoamine reuptake *in vitro* and accelerated release. This is similar to other piperazines derivatives (e.g. mCPP).

Effects on cardiovascular, respiratory, gastrointestinal, liver, kidneys and genitourinary systems
No study data available.

Behavioural studies in animals
No study data available.

Effects in humans
No study data available.

Interactions with other substances and medicines
Based on the limited pharmacological data for MeOPP, it is expected that an interaction with other substances that affect the monoamine systems might occur. In particular, other serotonin releasing agents and re-uptake inhibitors are likely to exacerbate the effects of MeOPP and vice versa. In the case of serotonergic compounds (e.g. most anti-depressants and MDMA), the development of a serotonin syndrome may be possible. Self-reporting users indicate poly-substance use is common as an intended adjunct to TFMPP or BZP use and many mention the additional use of these substances as well as other piperazines (e.g. mCPP).

4.2. Routes of Administration

As MeOPP is typically obtained in the form of a powder, tablet or capsule, the primary route of administration is oral consumption. However, it does not preclude the possibility of the powder being "snorted" or smoked which have been noted for BZP and other piperazines in self-reports on the Internet (Erowid and The Lycaeum). Intravenous use is also a possibility (as for amfetamines) but such a practice is rare. User reports and seizure data indicate doses for MeOPP to be typically between 50-500 mg, which is somewhat higher than many of the other substituted piperazines (Erowid, The Lycaeum; EMCDDA Early Warning System reports). In a test purchase from a UK-based website, two products were found to contain MeOPP: one with BZP and the other with BZP and pFPP (p-fluorophenylpiperazine). The two types of capsules, respectively, were white/pink and white/violet-purple, weighing 517 mg and 648 mg, with dimensions of 21.5mm x 7.5mm(cap) x 7.1mm(body). The capsules were unmarked.

4.3. Pharmacokinetics

Animal studies
In Wistar rats, MeOPP was found to be metabolised *in vivo* mainly by *O*-demethylation to 1-(4-hydroxyphenyl)piperazine (4-HO-PP) in addition to degradation of the piperazine moiety (Staack *et al.*, 2004). Staack *et al.* also studied the *O*-demethylation process with cDNA-expressed human hepatic cytochrome P450 enzymes in pooled

human liver microsomes and in single donor human liver microsomes with CYP2D6 poor metaboliser genotype. It was found that the CYP2D6 isoenzyme catalysed *O*-demethylation with apparent Km and Vmax values of 48.34 +/- 14.48 μM and 5.44 +/- 0.47 pmol min^{-1} $pmol^{-1}$ CYP, respectively. Pooled human liver microsomes catalysed the monitored reaction with apparent Km = 204.80 +/- 51.81 μM and Vmax = 127.50 +/- 13.25 pmol min^{-1} mg^{-1} protein. The CYP2D6-specific chemical inhibitor quinidine significantly inhibited 4-HO-PP formation by 71.9 +/- 4.8% (1 μM) and by 98.5% +/- 0.5% (3 μM), respectively, in incubation mixtures with pooled microsomes and 200 μM MeOPP. Furthermore, *O*-demethylation was found to be significantly lower in poor metabolising genotype microsomes compared with pooled microsomes (70.6% +/- 7.2%). This suggested the involvement of polymorphic CYP2D6 as the enzyme mainly responsible for MeOPP *O*-demethylation (Staack *et al.*, 2004). Based on the production of a hydroxy metabolite, glucuronide conjugation is likely (Maurer *et al.*, 2004).

In rat urine, 4-hydroxyaniline was detected in addition to 4-HO-PP (Staack *et al.*, 2003). The presence of these compounds may suggest MeOPP use, however, additional metabolites could be less specific and may be related to oMeOPP use. Furthermore, oMeOPP is a metabolite of some prescribed medicines: enciprazione, milipertine, urapidil, dropropizine and oxypertine (de Boer *et al.*, 2001; Staack and Maurer, 2003).

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and mutagenic/carcinogenic potential of MeOPP.

6. Adverse reactions in humans

Overall, user reports indicate MeOPP produces mild stimulant and some hallucinogenic effects. Additional adverse effects include nausea but no human studies have been performed and there are a very limited number of user reports, even on the Internet (Erowid and The Lycaeum). Although some user reports involve MeOPP alone, a few others also mention the use of other substances of abuse. This introduces the possibility of drug-drug interactions or exacerbation of toxic effects for poly-substance users. Abridged versions of these reports are as follows:

(i) 2003 (USA?) – 340 mg MeOPP as a powder. Mild calming effect noted after 1 hour post-dose. After 2 hours, "Feeling a mild body high, vision seems to waver on the peripheral, motion seems to be slowed down. There is no body chills....." "I'm a bit disappointed with this chemical, I don't think one can overdose on this unless he/she takes unheard of amounts (such as 1000-2000 mgs) overall, this is a great chemical for interacting with people, it does have mood lifting capabilities and makes you feel more emotionally open to others as well as yourself. Sense of humor seems to be sharpened, I can laugh at anything."

(ii) 2003 (unknown location) – 500 mg MeOPP as a powder. "After 20 mins or so I started to feel a little nausea, not bad compared to the nausea I've felt on other drugs, but still uncomfortable. After 15 mins of nausea it started to disappear and I started to feel a little more awake and things seemed all more pleasant, just like on speed, but not

as intense, also I felt some cold shiverings, very pleasant and some special intense sounds".

(iii) 2006 (unknown location) – 30 mg mCPP + 50 mg MeOPP. "After about an hour and a half, I felt a pretty decent euphoria that was not unlike an MDMA." Following occasional lethargy, the user then took additional mCPP (30 mg) and MeOPP (50 mg) and reported similar effects to MDMA but with no jaw clenching, nausea and pupils remained normal. A further 15 mg of mCPP and MeOPP was insufflated producing an extreme burning sensation but "kicked in pretty fast and increased the effects, mostly the visual components."

Cases of MeOPP intoxication in humans

There have been no reports of non-fatal or fatal intoxication where MeOPP has been detected. However, a major problem in investigating the involvement of MeOPP in hospital admissions and fatalities is the potential lack of laboratory confirmation or diagnosis. Although various methods have been published (Peters *et al.*, 2003; Staack and Maurer, 2003), MeOPP is not always included in routine or targeted toxicological analysis or may be detected but not identified as being MeOPP. Difficulties in determining the exact isomer present (i.e. oMeOPP or pMeOPP) may also be an analytical issue.

7. Dependence potential

No study data available.

8. Abuse potential

No study data available.

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

MeOPP has not been used in therapy.

10. Listing on the WHO Model List of Essential Medicines

MeOPP is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

MeOPP has never been marketed as a medicine.

12. Industrial use

MeOPP has no industrial use.

13. Non-medical use, abuse and dependence

Seized material containing MeOPP has been formally reported in the UK. However, Internet user reports suggest use in other countries (e.g. USA). The report on the WHO questionnaire for review of psychoactive substances for the 35th ECDD states that Denmark has reported 3 seizures from 2005 to 2007. Denmark reported that MeOPP is used, probably very limited, in a harmful way. 17 countries reported that it is not used in a harmful way and in 13 countries this is unknown.

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

As for BZP and TFMPP, MeOPP use appears to be associated with situations similar to that of "Ecstasy", or with users who are seeking effects similar to "Ecstasy" (MDMA in particular) and therefore instances of misuse, abuse and dependence would be limited to such individuals rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other piperazine-derivatives (e.g. BZP) or other substances. No fatal or other non-fatal intoxications of MeOPP (with or without other substances) have been reported.

15. Licit production, consumption and international trade

In the WHO questionnaire for review of psychoactive substance (annexe 1) Brunei indicated that they import the substance.

16. Illicit manufacture and traffic and related information

In the WHO questionnaire for review of psychoactive substance (annexe 1), there are no reports of illicit activities.

17. Current international controls and their impact

No current international controls under any of the international drug control conventions.

18. Current and past national controls

In the report on the WHO questionnaire for review of psychoactive substances (Annex 1) three countries reported that MeOPP is controlled under legislation that is intended to regulate availability of substances of abuse. While not included in the Standard for the Uniform Scheduling of Drugs and Poisons, the possession and supply of MeOPP is subject to control in certain Australian States and Territories, as a controlled substance. In Japan MeOPP is controlled as designated substances under the Pharmaceutical Affairs Law in Japan since April 2007.

Based on the recommendation of the EACD, the New Zealand government has passed legislation which placed BZP, along with the other piperazine derivatives TFMPP, mCPP, pFPP, MeOPP and MBZP, into Class C of the New Zealand Misuse of Drugs Act 1975. A ban was intended to come into effect in New Zealand on December 18th 2007, but the law change did not go through until the following year, and the sale of BZP and the other listed piperazines became illegal in New Zealand as of 1st of April 2008. An amnesty for possession and usage of these substances remained until October 2008, at which point they became completely illegal.

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

No data.

References

de Boer, D., Bosman, I.J., Hidvegi, E., Manzoni, C., Benko, A.A., dos Reys, L.J. and Maes, R.A. (2001) Piperazine-like compounds: a new group of designer drugs-of-abuse on the European market. Forensic Sci. Int., 121(1-2), 47-56

Erowid. Available from: http://www.erowid.org and http://www.erowid.org/chemicals

Lycaeum (the). Available from: http://leda.lycaeum.org

Maurer, H.H., Kraemer, T., Springer, D. and Staack, R.F. (2004) Chemistry, pharmacology, toxicology, and hepatic metabolism of designer drugs of the amphetamine (ecstasy), piperazine, and pyrrolidinophenone types: a synopsis. Ther. Drug Monitor., 26(2), 127-131

Minard, F.N., Cain, J.C., Grant, D.S. and Dren, A.T. (1979) N-o-Methoxyphenylpiperazine: a simple blocker of dopaminergic receptors in the brain. J. Pharm. Pharmacol., 31(2), 91-93

Moreno, I.E., da Fonseca, B.M., Magalhães, A.R., Geraldes, V.S., Queiroz, J.A., Barroso, M., Costa, S. and Gallardo, E. (2012) Rapid determination of piperazine-type stimulants in human urine by microextraction in packed sorbent after method optimization using a multivariate approach. J Chromatogr A. 1222, 116-20.

Nagai, F., Nonaka, R. and Satoh Hisashi Kamimura, K. (2007) The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. Eur. J. Pharmacol., 559(2-3), 132-7

Peters, F.T., Schaefer, S., Staack, R.F., Kraemer, T. and Maurer, H.H., (2003) Screening for and validated quantification of amphetamines and of amphetamine- and piperazine-derived designer drugs in human blood plasma by gas chromatography/mass spectrometry. J. Mass Spectrom., 38(6), 659-676

Staack, R.F. and Maurer, H.H. (2003) Toxicological detection of the new designer drug 1-(4-methoxyphenyl)piperazine and its metabolites in urine and differentiation from an intake of structurally related medicaments using gas chromatography-mass spectrometry. J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci., 798(2), 333-42

Staack, R.F., Theobald, D.S., Paul, L.D., Springer, D., Kraemer, T. and Maurer, H.H. (2004) In vivo metabolism of the new designer drug 1-(4-methoxyphenyl)piperazine (MeOPP) in rat and identification of the human cytochrome P450 enzymes responsible for the major metabolic step. Xenobiotica. 34(2), 179-92

Wohlfarth, A., Weinmann, W. and Dresen, S. (2010) LC-MS/MS screening method for designer amphetamines, tryptamines, and piperazines in serum. Anal Bioanal Chem. 396(7), 2403-14

ANNEX 1:WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD: 1-(4-methoxyphenyl)piperazine (MeOPP)

The 2008 WHO questionnaire for the preparation of the thirty-fifth Expert Committee on Drug Dependence was responded for 1-(4-Methoxyphenyl)piperazine (MeOPP) by 59 countries.

LEGITIMATE USE

Of the responded countries no country authorized MeOPP as a medical or veterinary product.

There are also no countries that legitimated MeOPP for technical use, nor is there any country who reported other legitimate use.

Brunei indicated that they import the substance.

ABUSE

Denmark reported that MeOPP is used, probably very limited, in a harmful way. 17 countries reported that it is not used in a harmful way and in 13 countries this is unknown.

Tuvalu indicated that they have not experienced any incident. There are no other countries who reported on the abuse of this substance.

CONTROL

3 countries reported that MeOPP is controlled under legislation that is intended to regulate availability of substances of abuse. In Australia, Denmark and Tuvalu this is controlled. Further there are no reports on illicit activities. However Denmark has reported 3 seizures from 2005 to 2007.

In Australia MeOPP is not subject to drug control regulations under Australian Customs legislation. While not included in the Standard for the Uniform Scheduling of Drugs and Poisons, the possession and supply of MeOPP is subject to drug control in certain Australian States and Territories, as a controlled drug. In Japan MeOPP is controlled as designated substances under the Pharmaceutical Affairs Law in Japan since April 2007. In Japan, it is called "4MPP".

IMPACT OF SCHEDULING

Considering the absence of any medical or veterinary use of the substance, there is unlikely to be any impact on medical services

Brand name - not applicable