Addiction Biology (2001) 6, 177–181

RESEARCH ARTICLE

Phenylalkylamine abuse among opiate addicts attending a methadone treatment programme in the Republic of Ireland

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Abstract

Since the early 1990s ring-substituted derivatives of amphetamine have been abused widely in the Republic of Ireland. The main ring-substituted amphetamines being abused include methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA) and methylenedioxyethamphetamine (MDEA). A newer illicit synthetic analogue, which has been seized to a lesser extent by Irish police, is N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB). The work presented here involved the determination of the type of ring-substituted amphetamines being abused by a group of recovering opiate abusers participating in a methadone maintenance programme in a Dublin Drug Rehabilitation Centre. Urine samples which tested positive for amphetamines and ring-substituted amphetamines via EMIT immunoassay were subjected to further analysis using GC-MS with MBTFA flash derivatization. It was found that the methylenedioxypropanamines were being abused, as was amphetamine itself. However, no abuse of methylenedioxybutanamines or thioamphetamines was observed.

Introduction

Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) were first synthesized in 1891[1] and 1910,[2] respectively (Fig. 1). Both MDMA and MDA were patented by E. Merck of Darmstadt in 1914.[3] After some abuse in the 1970s, MDMA disappeared as a drug of abuse, only to re-surface in the mid-1980s.[4] In the 1980s MDMA became known as "Ecstasy". This ring-substituted amphetamine fast became one of the most popular drugs of abuse among young people in Europe and the United States, where the drug was taken at parties featuring dance music, known as "raves". The acute and chronic toxicity of MDMA in humans is an area of controversy; however, numerous animal studies have shown toxicity[5,6] and there are a significant number of

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Received for publication 21st June 2000. Accepted 21st December 2000.

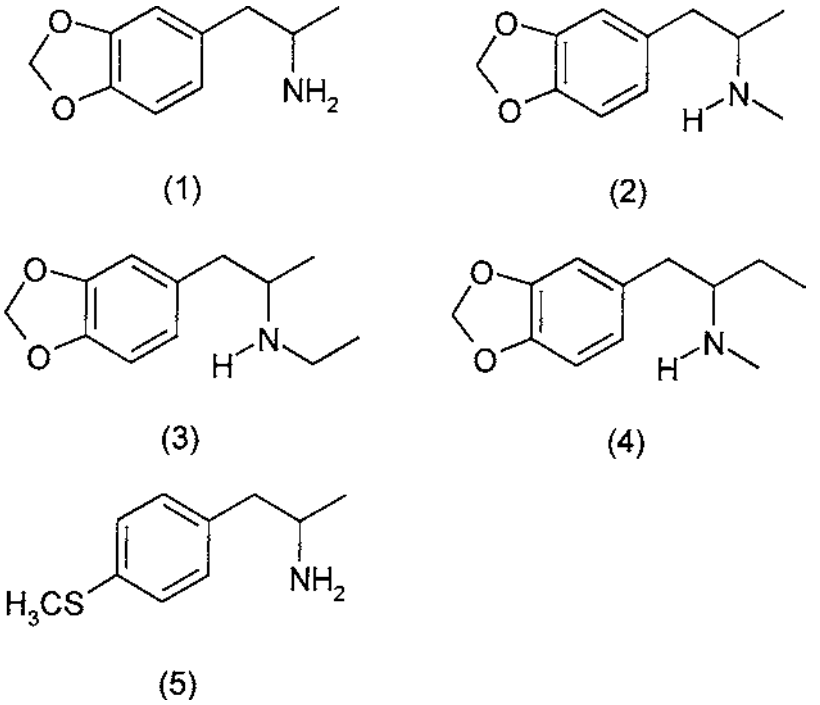

Figure 1. *Structures of (1) MDA, (2) MDMA, (3) MDEA, (4) MBDB and (5) 4-MTA.*

Ecstasy-related deaths.[7,8] MDMA and MDA have been controlled internationally since 1986 and 1990, respectively, under the terms of the 1971 United Nations Convention on Psychotropic Substances.[9]

Throughout the 1990s, new ring-substituted amphetamines began to appear on the illicit drug market. The motivation for these newer analogues was born out of an attempt to elude legislative control. The main analogues were methylenedioxyethamphetamine (MDEA) and N-methyl-l-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB) and more recently, to a much lesser extent, 4-methylthioamphetamine (4-MTA) (Fig. 1). The new synthetic analogues, or "designer drugs", were not controlled in many countries and therefore trading in these compounds was not illegal. As these drugs appeared, however, new drug legislation appeared simultaneously in an attempt to halt the manufacture, trafficking and sale of these drugs on the black market. As a result of the constant modification of the amphetamine backbone in an attempt to evade conviction, Ecstasy has become a generic name for tablets sold on the illicit drug market containing any of the aforementioned compounds and other non-amphetamine type compounds as adulterants and cutting agents.

MDA, MDMA, MDEA and MBDB are known collectively as the "entactogens". According to Nichols *et al.*,[10] who coined the term "entactogen", these drugs have the ability to "induce a state of reduced anxiety and lower defensiveness" and therefore considers them as having therapeutic potential. This aspect of the "entactogens" was exploited throughout the 1970s and 1980s by a small number of psychologists in the United States, in an attempt to reduce the trauma normally associated with the discussion of emotionally painful events.[4] Amphetamine, methamphetamine and 4-MTA do not belong to this class of drugs.

The main objective of this study was to determine the types of amphetamines being abused by a group of recovering heroin addicts attending a drug rehabilitation programme in Dublin. It is widely accepted that many heroin users are polydrug abusers and a precondition of the methadone programme is the abstention from opiates. However, other drugs such as ampheta-

mines and benzodiazepines are being abused.[11,12] Urine samples were taken from methadone clinic clients, who were all from the same locality. One hundred samples which tested positive for amphetamine/ring-substituted amphetamine abuse by EMIT immunoassay were subjected to extraction followed by MBTFA flash derivatization and subsequent GC-MS analysis. The main objective was to then determine the class of amphetamine being abused, be it conventional amphetamine, methamphetamine, methylenedioxypropanamines (MDA, MDMA or MDEA), methylenedioxybutanamines (BDB and MBDB) or 4-methylthioamphetamine (4-MTA). Of 100 samples, the presence of both amphetamine and MDMA/MDA was confirmed in 24 samples. Amphetamine was the only drug detected in 21 of 100 samples and MDMA/MDA was the only drug detected in 54 of the samples.

Materials and methods

Materials

Amphetamine and methamphetamine were part of an in-house drugs reference library. MDA, MDMA, MDEA, BDB, MBDB and 4-MTA were prepared at the Department of Pharmaceutical Chemistry, School of Pharmacy, Trinity College, Dublin. MBFTA, toluene, ammonia, methanol, ether and diphenylamine were supplied by Aldrich, Dorset, UK. EMIT DAU monoclonal amphetamine/methamphetamine (Dade Behring) was used according to the manufacturers' instructions.

Sample collection and storage

Urine samples were collected as part of normal drugs of abuse screening at the Drug Treatment Centre, Pearse Street, Dublin, during July and August 1999. One hundred samples which had tested positive for Amphetamines by EMIT immunoassay were stored at −20°C until GC-MS analysis.

Sample preparation

A 10-µl aliquot of diphenylamine (10 mg/ml in methanol) was added to 2 ml of EMIT-positive urine. This was made alkaline with conc. aqueous ammonia (0.5 ml) and extracted with 2 ml of ether. The ether extract was then evaporated to dryness and the residue was reconstituted in toluene (80 µl). MBTFA (20 µl) was then added. Standards containing amphetamine, methamphetamine, BDB, MBDB, MDA, MDMA, MDEA and 4-MTA (2 µg/ml) were prepared in drug-free urine and extracted as above.

GC-MS conditions

The system consisted of a Hewlett Packard 5973 MSD coupled to a 6890 GC system and a 6890 Injector Autosampler. A Hewlett Packard HP-5MS column (30 m × 0.25 mm × 0.25 µm film thickness) was used with the following conditions: carrier gas, helium 1 ml/min; 90°C for 1 min, 15°C/min to 280°C, 280°C for 6 minutes, injector port, 260°C, transfer line, 280°C. The mass range was 40–600 Da/e. Injections were carried out in splitless mode.

Results and discussion

In the Republic of Ireland, the extent of ring-substituted amphetamine abuse exceeds that of the none-substituted form. Amphetamine abuse among first-contact patients of the drug treatment programme in 1997 and 1998 in the Dublin area was approximately 1%.[13] This low level of amphetamine abuse has been a feature of the drug scene in Ireland since the 1970s.[14] The extent of ring-substituted amphetamine abuse for first-contact patients for the same region was 4.8% in 1997 and 3.7% in 1998.[13]

Using the GC-MS system outlined, relative retention times were determined for each of the standards which had been extracted from drug free urine (Table 1). The most significant ions in each of the standard mass spectra were recorded (Table 1).

As MDMA and MDEA are known to be metabolized via *N*-dealkylation, MDA is an expected metabolite in any sample containing MDMA or MDEA.[15,22] It follows that it is therefore not possible, in this situation, to determine whether or not MDA was present in the initial drug formulation. The absence of the *N*-alkylated parent drug would, however, indicate that MDA was most probably present in the initial formulation. For the same reasons the occurrence of BDB is indicative of the use of either BDB or of MBDB,[15] but it is difficult to say whether BDB itself was in the initial formulation when it is detected along with MBDB. Further, amphetamine may only be present in

Table 1. *Relative retention times for trifluoracetyl derivatives of analytes and their respective significant fragment ions*

Analyte (TFA derivative)	Relative retention time	Mass ion
Amphetamine	0.70	91, 118, 140
Methamphetamine	0.81	110, 118, 154
MDA	1.02	135, 162, 275
BDB	1.09	135, 176, 289
4-MTA	1.10	137, 164, 277
MDMA	1.13	154, 168, 289
MDEA	1.17	162, 168, 303
MBDB	1.18	168, 176, 303
Internal standard	1.00	168, 172, 265

samples of methamphetamine as a metabolite and not as a true drug constituent.

In 21 of 100 samples analysed, amphetamine was the only drug detected. MDMA/MDA was the only significant substituted amphetamine in 54 of the 100 samples. However, 24% of the samples showed both amphetamine and MDMA/MDA. This finding backs up the previously mentioned prevalence of ring-substituted amphetamines with respect to the non-substituted amphetamines abuse. There was one incidence of the anorectic, phentermine, in the samples analysed (Fig. 2). The adverse effects of MDMA were reviewed[5] and the possibility of acute cardiac and neurological effects, leading to death, have been documented. It is possible that the combined use of amphetamine with MDMA/MDA could add to the risks associated (such as toxicity and accident injury/death) with taking ecstasy alone.

The fact that there were no BDB, MBDB or MDEA present was not surprising as Irish Police

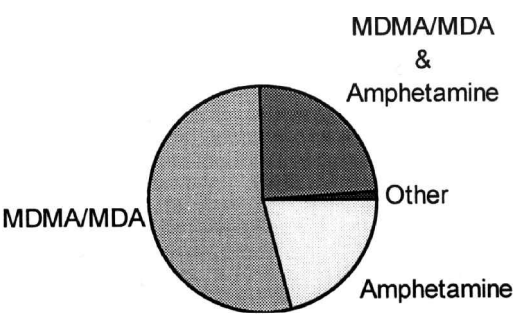

Figure 2. *Pie chart representing the metabolites found in urine samples using GC.*

(*An Gardai*) records reflect this observation. It would appear that the majority of "Ecstasy" seized in the Republic of Ireland in 1998 was almost exclusively MDMA and only a fraction of cases involved MDEA and MBDB.[16] In that same year, there were no reported seizures of BDB.

In Germany MDMA and MDEA seem to be the most significantly abused, with little MBDB or MDA being encountered.[17] It is also reported that 95% of all drugs sold as "Ecstasy" in Germany contain only one compound and that only 5% of formulations appeared as mixtures, which may give anecdotal credence to the possibility that the MDA in the samples was of metabolic origin. However, King[18] described the significant occurrence of MDA, MDMA and MDEA in the United Kingdom with some samples seen as mixtures of MDMA with MDEA and MDMA with MDA.

It has been shown in the past that 4-MTA cross-reacts with the particular immunoassay system that was employed here.[19] The absence of 4-MTA was due probably to the limited number of seizures in Europe, coupled with the high incidence of 4-MTA associated fatality,[20] which may have led to a decline in its use. Although not particularly renowned for its abuse potential the appetite suppressant, phentermine, will rarely induce euphoria but can cause insomnia.[21] The occurrence of the phentermine positive sample highlights the potentials for cross-reactivity in immunoassay systems and bolsters the need for reliable, confirmatory but expensive GC-MS procedures. It has been shown that both amphetamine and MDMA/MDA abuse can be con-

firmed by GC-MS with trifluoroacetyl derivatization and that such abuse is occurring in the clients of the Dublin methadone programme.

Conclusion

A rapid GC-MS procedure incorporating flash derivatization has been established for a series of amphetamines and their analogues which can be used in urinalysis to identify the type of amphetamines being abused. The results provide epidemiological data for a small group of drug users, in one locality, in the Republic of Ireland. The group studied would most probably be exposed to the same market trends as the general population. This would indicate that the methylenedioxypropanamines, which have been around for many years, and not newer analogues such as thioamphetamine and butanamines, are most probably the main ring-substituted amphetamines available.

References

1. Haber F. Veber einige derivate des piperonals. Ber Dtsch Chem Ges 1891;24:617–26.
2. Mannich C, Jacobson W. Uber Oxyphenylalkylamine und Dioxyphenylalkylamine. Ber Dtsch Chem Ges 1910;43:1891.
3. E. Merck of Darmstadt, assignee. Patent. Germany patent 274, 350. 1914 May 16.
4. Grob C. MDMA research: preliminary investigations with human subjects. Int J Drug Policy 1998;9:119–24.
5. McCann UD, Slate SO, Ricaurte GA. Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy"). Drug Experience 1996;15:107–115.
6. McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings. Lancet 1998;352:1433–7.
7. Lora-Tamayo C, Tena T, Rodriguez A. Amphetamine derivative related deaths. Forens Sci Int 1997;85:149–57.
8. Tsatsakis AM, Michalodimitrikis MN, Angelo JD, Patsallis N. MDEA related death in Crete: a case report and literature review. Vet Hum Toxicol 1997;39:241–4.
9. http://www.incb.org/e/conv/1971
10. Nichols DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. J Psychoact Drugs 1986;18:305–313.
11. Best D, Harris J, Gossop M, Farrell M, Finch E, Noble A. Use of non-prescribed methadone and other illicit drugs during methadone maintenance treatment. Drug Alcohol Rev 2000;19:9–16.
12. Browne R, Sloan D, Fahy S, Keating S, Moran C, O'Connor J. Detection of benzodiazepine abuse in opiate addicts. Irish Med J 1998;91:18–19.
13. Corrigan D. Facts about drug abuse in Ireland., 3rd edn. Dublin: Department of Health (Health Promotion Unit); 1991, revised 1994.
14. O'Brien M, Moran R, Kelleher T, Cahill P. National drug treatment reporting system statistical bulletin. Dublin: Health Research Board: Drug Misuse Research Division; 2000.
15. Maurer H. On the metabolism and the toxicological analysis of methylenedioxyphenylalkylamine designer drugs by gas chromatography-mass spectrometry. Ther Drug Monitor 1996;18:465–70.
16. An Garda Siochana Annual Report 1998: Drugs offences: 92–96.
17. Sondermann NK, Kovar KA. Identification of ecstasy in complex matrices using near-infrared spectroscopy. Forens Sci Int 1999;102:133–47.
18. King LA. Drug content of powders and other illicit preparations in the UK. Forens Sci Int 1997;85:135–47.
19. Kavanagh PV, Corrigan D, Maguire RT *et al*. Excretion profile of 4-methylthioamphetamine in dogs. Pharm Pharmacol Commun 1999;5:653–5.
20. EMCDDA. Report on the risk assessment of 4-MTA in the framework of the joint action on new synthetic drugs. Luxembourg: Office for Official Publications of the European Communities; 1999.
21. Perrine DM. The chemistry of mind-altering drugs: history pharmacology and cultural context, 1st edn. Washington, DC: American Chemical Society; 1996.
22. Helmlin HJ, Bracher K, Bourquin D, Vonlanthin D, Brenneisen R. Analysis of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites in plasma and urine by HPLC-DAD and GC-MS. J Analyt Toxicol 1996;20:432–440.