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Abstract: 5-MeO-DALT (N,N-diallyl-5-methoxytryptamine) is a psychoactive substance, sold primarily over the Internet as a 'research chemical' or 'plant food'. Although details for the synthesis of this tryptamine have been available since 2004, its use as a hallucinogenic drug has been reported only occasionally in on-line user fora. It is controlled in only a few countries world-wide. There is little scientifically-based literature on the pharmacological, physiological, psychopharmacological, toxicological and epidemiological characteristics of 5-MeO-DALT. Here we review what is known about these aspects. We also report what we believe to be the first death involving the use of this substance. The case involved a man in his mid-20s who died in mid-2010. The coroner concluded that the deceased "died from injuries sustained after being hit by a lorry whilst under the influence of 5-MeO-DALT". It is critical that any other cases, including non-fatal instances, are documented so that a scientific evidence-base can be established for this drug.

Ethical Statement

No ethical approval was required as the subject was deceased.

Highlights

- 5-MeO-DALT is a psychoactive substance, sold mainly on Internet as a ‘research chemical’
- Use as a hallucinogenic is reported occasionally in on-line user fora; it can affect risk assessment
- Scant scientific literature on physical effects, psychopharmacology, toxicology
- Victim died from injuries sustained when hit by a vehicle whilst under its influence
- Any other (non-) fatal cases need documenting to establish scientific evidence-base

The recreational tryptamine 5-MeO-DALT (N,N-diallyl-5-methoxytryptamine): a brief review

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Running title:
Review of 5-MeO-DALT

Main text

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List of abbreviations:

5-MeO-DALT = N,N-diallyl-5-methoxytryptamine;
(N-allyl-N-[2-(5-methoxy-1H-indol-3-yl)ethyl]prop-2-en-1-amine)
5-MeO-DiPT = 5-methoxy-diisopropyltryptamine
AMT = Alpha-methyltryptamine
DALT = N,N-Diallyltryptamine
MAO-A = Monoamine oxidase A
MAO-B = Monoamine oxidase B
MDMA = 3,4-methylenedioxy-N-methylamphetamine

The recreational tryptamine 5-MeO-DALT (N,N-diallyl-5-methoxytryptamine): a brief review

1 Introduction

1.1 Tryptamine is a naturally occurring monoamine alkaloid found in plants and fungi. Chemically related to tryptophan, an amino acid, it is founded on the indole ring structure. Mammalian brains contain trace amounts of the substance which may act as a neurotransmitter or modulator (Jones, 1982), is a serotonin releasing agent (Wölfel and Graefe, 1992), and serotonergic activity enhancer (Shimazu and Miklya, 2004), being metabolised by MAO-A and MAO-B (Sullivan et al., 1986). Chemical variants of naturally occurring tryptamines are obtained by modifying a side-chain or functional group.

1.2 5-MeO-DALT (N-allyl-N-[2-(5-methoxy-1H-indol-3-yl)ethyl]prop-2-en-1-amine; N,N-diallyl-5-methoxytryptamine) is very closely related chemically to the compounds 5-MeO-DiPT (5-methoxy-diisopropyltryptamine) and DALT (N,N-Diallyltryptamine) (Figure 1) and was first synthesised by Alexander Shulgin (Shulgin and Shulgin, 2010). The manufacturing instructions contained in his book can easily be found on the Internet.

< Figure 1 here>

1.3 It appears that drug users did not widely use this new substance. The Psychonaut Project in 2002 revealed 5-MeO-DALT as one of a new group of tryptamines (Indolalkylamines) being experimented with by psychonauts, i.e. those who explore their own psyche especially by taking psychedelic or hallucinogenic substances (Schifano et al., 2006). According to the European Database on New Drugs (EDND), it was first seen (as two grey tablets) in a Customs seizure at Helsinki airport, Finland, in December 2006, of a postal package with apparent Danish origins. The second report was the present death. Since then, German police seized 687g powder in June 2010, Swedish police seized 0.8g of a dried herbal substance in January, 2011, UK police seized a green mixture containing several substances including 5-MeO-DALT at a 'headshop' in March 2011, the Bulgarian authorities seized a capsule in May 2011, and Belgian police seized three minigrip bags at a Brussels Internet shop in August 2011: one contained 20.3g beige powder (with traces of methylone) and two contained 18.7g and 19.0g respectively of white powder (EDND, 2011). The EDND does not contain any information on the purity levels of these samples, all confirmed analytically. This substance seems to have been hardly used, known about generally, e.g. through general household or user surveys, or encountered by law enforcement and forensic science agencies or Emergency Rooms. This is especially true in the UK. For these reasons, there is very little scientific information about the drug, its pharmacology, metabolism, effects, toxicity, and epidemiology.

2 Availability

2.1 Originally advertised as a 'plant fertiliser' or 'plant food' but more recently as a 'research chemical', 5-MeO-DALT comes as a salt or in free-base form. It was said by some consumers in 2004 to be 'clumpish'/'sticky' but retail websites now make a point of describing it as free-flowing, with a slight smell, and its colour ranging from white to light-brown/tan. In February 2010 contributors to the BlueLight on-line discussion forum began suggesting that there were different 'batches' of 5-MeO-DALT in circulation (Bluelight, 2010). In September 2010, Erowid (the online library of information on psychoactive plants and chemicals) had analysed two samples

submitted to them following purchase from Internet sites. One sample proved to be very pure 5-MeO-DALT, but the second appeared to be flephedrone (4-fluoromethcathinone) (Erowid and Spoon, 2010). A brief opportunistic Internet search at the end of September 2011 revealed that supplies of 5-MeO-DALT could be ordered in amounts ranging from 500mg to 20kg. Prices for European consumers ranged from €17 - €29 (US$23 - US$39) for 1g (sufficient for 40 to 50 doses) up to €4600 – €5400 (US$6200 - US$7300) for 1 kg. Prices were considerably higher – up to 5 times – for US consumers (as with other drugs). Websites advertising 5-MeO-DALT usually display a disclaimer to the effect that it is "not for human consumption", or that the "chemicals are only to be used by laboratories, scientific institutions and some science enthusiasts for private testing". Clients also allegedly have to be aged 18 years or older.

3 Legal status

3.1 There are no international controls, i.e. UN conventions, imposed on 5-MeO-DALT. The substance is not scheduled in the USA. As an allyl-substituted tryptamine, 5-MeO-DALT does not come within the generic definition of a (Class A) substituted tryptamine under the Misuse of Drugs Act 1971 in the UK; it would do if it was an alkyl group. However, it is now a controlled substance in Bulgaria, Finland and Romania (EDND, 2011). In Japan, it is now regulated as a 'designated substance' in terms of its importation, synthesis, and sale (Kamata et al., 2010).

4 Route of administration

4.1 There are several known routes of administration: insufflation (snorting, sniffing); intravenous injecting; oral (swallowing in a capsule, wrapped in a cigarette paper 'bomb', or washed down with fruit juice); rectal; and vapourisation (inhalation) (Drugs Forum, 2010). Shulgin and Shulgin (2010) recommended oral doses from 12 to 25 mg for normal use, although initial doses of up to 50mg have been reported (Bluelight, 2010; Erowid, 2010). Oral ingestion appears to be the usual route of administration.

5 Pharmacology

5.1 There is a close structural likeness between serotonin and tryptamine. Tryptamines generally are hallucinogenic compounds, increasing the release of serotonin and inhibiting its reuptake. The structural similarities of synthetic tryptamines to serotonin may give rise to similar effects (Gibbons, 2012).

5.2 There is little information on the pharmacodynamics and pharmacokinetics of 5-MeO-DALT. In vitro research on rat brains has demonstrated that this substance appears to elicit G protein activation via serotonin 5-HT_1 (5-hydroxytryptamine) receptors (Nonaka et al., 2007). It appears to have no detectable effect on dopamine, 5-HT or norepinephrine re-uptake; and only slight monoamine-releasing activity (Nagai et al., 2007). Although the affinity of 5-MeO-DALT to specific 5-HT receptors has not been investigated, the related substance 5-MeO-DiPT has shown in vitro affinity for the 5-HT1A receptor, but less so for the 5-HT2A and 5-HT2C receptors (Fantegrossi et al., 2006). Also, 5-MeO-DALT has been shown to be a competitive inhibitor of the Serotonin reuptake transporter (SERT) (Sogawa et al., 2007; Nagai et al., 2007).

5.3 Although the metabolism of 5-MeO-DALT has not been explored that of a closely related tryptamine analogue 5-MeO-DIPT has been recently examined, with three main metabolites having been identified as 5-hydroxy-N,N-diisopropyltryptamine (5-

OH-DIPT); 6-hydroxy-5-methoxy-N,N-diisopropyltryptamine (6-OH-5-MeO-DIPT), and 5-methoxy-N-isopropyl-tryptamine (5-MeO-NIPT) (Kamata et al., 2010). Similar metabolic pathways have been found for other tryptamine-derived hallucinogens; it may be, therefore, that similar pathways exist for 5-MeO-DALT.

6 Effects

6.1 Most of the information published on the effects of 5-MeO-DALT is derived from first-hand personal accounts presented in discussion fora. User reports suggest that its effects are felt within 15 minutes of being taken orally, and its full effects within 30 minutes. This, according to Shulgin and Shulgin (2010), suggests absorption into the blood stream directly from the stomach and rapid metabolism. User reports on 5-MeO-DALT state rapid, strong entheogenic effect, euphoric, sensual, energised bodies, visual hallucinations (similar to those experienced with MDMA), loss of control of limbs making walking difficult, and 'out of body' type experience (Erowid, 2010). Some users on low doses have reported no after effects. The main effects of the substance last for 2 - 4 hours, but the visual effects persist for a while longer (Erowid, 2010). The intensity of such effects appears to be dose-related (Erowid, 2010).

6.2 Self-reported acute physical effects, unsubstantiated by medical observation, may include: vaso-constriction, increase in blood pressure, rapid heart-beat, headache, and sweating. Other side-effects reported include: the urge to eat ('munchies'), dilated pupils, tension in the neck and jaw (bruxism), slight paranoia or anxiety, nausea (Erowid, 2010). Acute mental effects reported include: increased alertness and awareness; increased arousal; and agitation (Erowid, 2010).

7 Toxicity

7.1 According to Nichols (2004), the tryptamine class are normally unlikely to "cause life-threatening changes in cardiovascular, renal or hepatic function because of their lack of affinity for the relevant receptors and targets". However, the consumption of alpha-methyltryptamine/α-methyltryptamine (AMT) and/or 5-MeO-AMT ('foxy') has been associated with US fatalities (Boland et al., 2005). Whilst the clinical effects of tryptamine are similar when a methoxyl (or hydroxyl) group is added at position 5 of the tryptamine ring, there is also increased potency (Rogawski and Aghajanian, 1981). 5-substituted tryptamines such as 5-methoxy-diisopropyltryptamine (5-MeO-DiPT) have been implicated in death. An individual with known polyarteritis nodosa died of acute cardiac failure due to neurotoxicity caused by an overdose of this drug (Tanaka et al., 2006). There are also case reports of hallucinations and paranoia (Wilson et al., 2005). The hallucinogenic effects of such tryptamines may lead to disturbances in behaviour, resulting in life-threatening situations (Peden et al., 1981).

7.2 Despite the time-period during which 5-MeO-DALT has been on the scene there is no information on its long-term effects. There have been no previously reported deaths from 5-MeO-DALT, although there has been at least one admission to hospital for observation following a particularly unpleasant 'trip' (Drugs Forum, 2010), and an overdose within 3 months of Shulgin releasing the recipe on his website in May 2004. The US victim had ingested 225mg of the drug (Kamata et al, 2010). Its safety profile is unknown. No definitive concentrations of 5-MeO-DALT have been established for toxic effects or death.

8 Fatality involving 5-MeO-DALT

8.1 Notification

8.1.1 The National Programme on Substance Abuse Deaths (np-SAD) receives information on a voluntary basis from coroners in the United Kingdom concerning inquests completed on drug-related deaths (Ghodse et al, 2010). Here we present a report on a death in which the presence of 5-MeO-DALT was identified alongside ethanol detection. This case was notified in December 2010 as part of routine data submission. Additional information was provided by HM Coroner in the form of the autopsy and toxicology reports.

8.2 Events leading to death

8.2.1 In July 2010, a single white male in his mid-twenties, was seen to walk out into the slow lane of a motorway in front of a heavy goods vehicle at 02:00 hrs. He was hit by the vehicle, sustaining injuries to his skull. Ambulance personnel attended but despite extensive treatment the male's death was confirmed at 03:15 en route to hospital. The driver described how the deceased was continually grinning whilst walking on the motorway. At the inquest it was reported that he had earlier snorted 350mg of 5-MeO-DALT (when the normal dose is 25mg) in a public house with a friend who had purchased 1g of it over the Internet for £20 (US$31, €23). The deceased described it as making him feel "pretty good". He and his friend had been discussing trying 'legal highs' for several weeks prior to the incident. The deceased had no medical history of note.

8.3 Autopsy

8.3.1 The autopsy, conducted about 33 hrs after death, found the deceased had sustained a significant head injury with a base of skull fracture and cerebral contusions, together with significant pulmonary contusions. There was no significant underlying natural pathology. The pathologist in this case recorded the cause of death as "fractured base of skull".

8.4 Toxicological investigation

8.4.1 As part of a general (non-targeted) screening protocol, an initial toxicological investigation using high performance liquid chromatography with UV-diode array detection (HPLC-DAD) found that the post-mortem femoral blood contained an atracurium breakdown product (laudanosine) and propofol; their presence is consistent with medical intervention at the scene and on the way to hospital. The blood alcohol concentration was 22 mg/dL, indicating the consumption of alcohol at some point prior to death. A compound was detected in the blood with a distinctive tryptamine-like UV spectrum. Tryptamine itself is regularly observed as a putrefactive compound. No other drugs were detected, including purported "Legal Highs" such as piperazines and cathinones.

8.4.2 Following the provision of further information about the deceased's consumption of 5-MeO-DALT, supplementary toxicological analysis was undertaken of the post mortem femoral blood samples. This was performed using liquid chromatography with mass spectrometry detection (LC-MS) as it can be difficult to distinguish between tryptamine and other naturally occurring tryptamine-related compounds and those with methoxytryptamine derivatives (including 5-MeO-DALT) with similar UV spectra. Primarily based on the pseudo molecular ion (MW = 270.3694, [M+H] = 271.37) with supporting mass fragmentation, LC-MS analysis indicated the compound was 5-MeO-DALT. This was later confirmed following analysis of pure reference material. However, due to the time for the standard to

become available, it was not possible to measure the compound in the blood within the Coronial inquest period.

8.5 Coroner's verdict

8.5.1 The Coroner returned a narrative verdict on 28 October 2010: "He died from injuries sustained after being hit by a lorry whilst under the influence of 5-MeO-DALT". He added, "It is a tragedy when anybody who takes drugs dies because of it, especially when it is a substance easily purchased from the Internet and purchased legally in this case" (Makey, 2010).

9 Discussion

9.1 The experiences and effects of 5-MeO-DALT are similar to those reported by users of other tryptamines, methylenedioxypyrovalerone (MDPV) and some methcathinone analogues (Schifano et al., 2006). Importantly, it appears to act as a hallucinogen and can alter perception, including the assessment of risk. Use of this substance may therefore increase the possibility of poor assessment of situations, resulting in accidents (Gibbons, 2012); for example, as described in the case described here and that reported by Wilson et al. (2005)..

9.2 Since 5-MeO-DALT has similar UV spectra as naturally occurring tryptamines, it is important that forensic toxicologists and Emergency Department physicians do not overlook the possibility of the ingestion of recreational tryptamines. Whenever possible, full details should be obtained of the circumstances leading to hospitalisation or death so that the appropriate toxicological investigations and medical interventions are performed.

9.3 At the time of writing, no poisonings or fatalities involving 5-MeO-DALT have been reported in the scientific literature. Indeed, this paper is believed to be the first such article to describe a fatality in which the presence of 5-MeO-DALT was recorded. There is no reliable relevant pharmacokinetic information on 5-MeO-DALT in terms of lethal dosage, half-life, volume of distribution, etc. Fatalities involving tryptamine analogues appear to be very rare events and thus there is limited published evidence which can be used to inform cases such as the present one with respect to closely-related tryptamines; one fatality in Japan involved 5-MeO-DiPT ingestion. The decedent had been given a rectal administration of the substance to enhance his sexual experience. He became very agitated, was taken to hospital but died 3.5 hrs later. The cause of death was considered to be acute cardiac failure due to an overdose of the drug (Tanaka et al., 2006).

9.4 It is difficult to keep abreast of the new products being created by 'research chemists', which warrants establishment of a readily accessible forensic toxicology database of samples of new psychoactive substances.

10 Conclusions

10.1 This paper has outlined what is presently known about 5-MeO-DALT. It has also described what we believe to be the first death in the UK, and probably world-wide, involving the presence of the drug 5-MeO-DALT and which contributed to death. Due to its relatively recent emergence on the scene, its lack of widespread use, unknown toxicity and lack of detection through routine toxicological screens, use of this substance could be missed by clinicians. Similarly, fatalities involving this substance may be overlooked by those investigating sudden deaths with no apparent cause(s). Determination of the significance and role in death, if any, has to be provisional and

delivered with caution, qualifications and reservations. Without the additional information provided by the decedent's companion, this UK fatality could have been recorded as 'accidental' due to injuries sustained in road traffic accident and alcohol intoxication.

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Conflict of interest

We are unaware of any conflict of interests.

Declaration

This work has not been previously published and has not been submitted for publication elsewhere. Publication is approved by all authors and the responsible authorities where the research was undertaken. If accepted, the paper will not be published elsewhere in the same form, in English or in any other language, without the written consent of the copy-right holder.

Contributors

John Corkery undertook data collection and preparation. Emma Durkin and Simon Elliott were involved in the toxicological analysis of the case-study. All authors contributed to the writing of the paper.

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Figure

Figure 1: Chemical structure of 5-MeO-DALT and related substances

5-MeO-DALT (N,N-diallyl-5-methoxytryptamine ; N-Allyl-N-[2-(5-methoxy-1H-indol-3-yl)ethyl]-2-propen-1-amine)	*Tryptamine (2-(1H-Indol-3-yl)ethanamine)*	*5-MeO-DiPT (5-Methoxy-N,N-Diisopropyltryptamine(5-MeO-DIPT) ; N-Isopropyl-N-[2-(5-methoxy-1H-indol-3-yl)ethyl]-2-propanamine)*