Toxicity of drug abuse — amphetamine designer drugs (ecstasy): mental effects and consequences of single dose use

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Abstract

MDMA (3,4-methylendioxymethamphetamine) is the most commonly used substance within the ‘ecstasy’ group of drugs. MDMA interferes with serotonin and catecholamine transporters in the central nervous system to increase monoamine synaptic levels and thereby mediate the majority of its central nervous effects. These range from wanted effects like euphoria, central nervous stimulation, and feeling of closeness to mild hallucinations, impairment of cognition and co-ordination and further to serious reactions like agitation, disturbed and bizarre behaviour, and possibly psychosis. The full picture of the consequences of these transitory changes is not known. It has been assumed that the risk of being involved in fatalities and accidents during the state of MDMA influence is increased, but this possible risk increase has so far not been determined. Observations of the prevalence of MDMA involvement in cases of reckless driving and the MDMA blood concentrations measured indicate a risk increase comparable to that observed after use of amphetamines. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

In this review paper some mental effects occurring during the influence of ecstasy (MDMA), i.e. the acute effects, will be presented and discussed in relation to possible deleterious consequences of such effects, specially with respects to accidents. Such effects should also be regarded as toxicological, although different from other more traditional problems related to long lasting changes of cell biochemistry. The important point is that a drug with fully reversible effects as MDMA, might, during its period of action, cause effects which might lead to secondary, long-lasting consequences. One example of this is cerebral haemorrhage due to increase blood pressure, another is severe accidents occurring as a consequence of the influence of the drug on the central nervous system.

In the following, neurobiological primary effects of MDMA will be presented. The mental and behavioral effects during MDMA influence will then be briefly reviewed. Finally the consequences of these effects with respect to the risk of accidents will be discussed.

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2. Neurobiological acute effects

The main effects of MDMA in the central nervous system are mediated by changed monoaminergic neurotransmission. These effects have recently been reviewed by White et al. (1996). Neurochemical studies performed in vitro have demonstrated that MDMA induced the release of serotonin (5HT) from brain synaptosomes, and similar effects have been found for dopamine (DA) and norepinephrine (NE). MDMA is a more potent releaser of 5HT than DA in vitro, releasing 5HT from striatal slices at concentrations about 10-fold lower than those that were required to stimulate DA-release (Schmidt et al., 1987). The release of 5HT appears to be connected to MDMA interaction with the 5HT-transporter in several in vitro systems, as the release can be blocked by fluoxetine or imipramine which are inhibitors of the 5HT transporter (Berger et al., 1992; Rudnick and Wall, 1992). It has been suggested that MDMA induces monoamine release by interacting with the monoamine carriers to reverse the direction of the neurotransmitter flow (Heckmatpanah and Peroutka, 1990). Accordingly, MDMA also increase extracellular levels of 5HT, DA and NE by inhibition of their re-uptake. In addition it has also been shown that MDMA inhibits brain monoamine oxidase (MAO). Thus, MDMA might increase the synaptic monoamine level by at least three different mechanisms: increased release, inhibited uptake (both related to action on the transporters) and by MAO-inhibition. A major mechanism by which MDMA may actually affect neuronal excitability in the brain is therefore by increasing extracellular levels of 5HT, DA and NE for the period MDMA is present at a sufficient concentration, and thereby activating 5HT-, DA- and NE-receptors during this period.

In principle all synapses where serotonin and catecholamines are involved could be influenced by MDMA in this way. In vivo studies in animals, applying microdialysis and voltametry techniques, have actually demonstrated DA-increases in Striatum and in Mesolimbic dopaminergic structures such as Nucleus Accumbens and VTA. 5HT does also increase in these structures after administration of MDMA, but to a lesser extent than DA. On the other hand it appears that the 5HT increase is at least partially responsible for the DA-increase observed.

These neurochemical changes have been regarded as being of central importance to the rewarding properties of MDMA, as well as to to the locomotor hyperactivity observed after intake of the drug. MDMA-induced increases of extracellular 5HT in the dorsal raphe nucleus might modulate these effects. Increases in 5HT are also considered to be of central importance to the development of hypothermia and the so-called serotonin syndrome in animals and man.

3. Mental and behavioral effects during MDMA influence

Neurobiological studies have indicated that MDMA might have some important differences from amphetamines with respect to mechanisms of action, as 5HT is influenced in addition to DA and NE by MDMA. Accordingly, researchers have been looking for another profile of mental and behavioral effects caused by MDMA than that caused by amphetamines. One major problem which is encountered when this question is approached is the almost complete lack of controlled, randomized (placebo, cross-over) studies with MDMA in humans. Due to the illegal status for MDMA and because of fear of toxicological consequences future controlled studies with MDMA in doses taken by drug-users will probably not be performed.

A controlled cross-over study has recently been published (Henry et al., 1998), but the MDMA-dose was low (40 mg) and no central nervous effects were reported or recorded. Yet another controlled study with a related ecstasy compound, MDEA (150 mg) and placebo was recently published (Schreckenberger et al., 1998). In this study regional decreases of cerebral glucose metabolism were observed in the frontal cortex and some other brain regions, similar to what has been observed after intake of other psychotropic substances. No mental or behavioral measures appeared to have been studied in this report.
We are accordingly left with two types of information sources on acute MDMA-effects: (1) systematic studies on recreational drug users and (2) medical case histories from subjects requiring medical attention after MDMA use.

Both these sets of information are, however, complicated to interpret with respect to the ‘pure’ acute effects of MDMA, as they often present results that are a consequence of combined single dose and chronic use (often of unknown magnitude), with uncertain degrees of tolerance, sensitizations and other long-lasting effects from previous use, being present together with the acute effects under study. Another complicating fact is that in many cases, present and previous use of other drugs than MDMA will be present.

3.1. Systematic studies on acute mental and behavioral effects of MDMA

Parrot and Lasky (1998) studied three groups of young people (aged 19–30 years): 15 regular MDMA users who had taken the drug on ten or more occasions; 15 novice MDMA users who had taken MDMA on fewer than ten previous occasions; and 15 controls who had never taken MDMA, but other drugs. Each subject completed a cognitive test and mood scale battery four times: An initial drug-free baseline, at a Saturday night dance club (on drug), then 2 and 7 days later. All three groups used alcohol and other drugs at the dance club, and all reported positive moods (on-drug). However, 2 days afterwards the MDMA-users felt significantly more depressed, abnormal, unsociable, unpleasant and less well-tempered than the controls. Cognitive performance on both tasks (vocal recall, visual scanning) was significantly reduced on MDMA compared to controls. Memory recall was also significantly impaired in ‘drug-free’ MDMA-users, with regular users displaying the worst memory scores at every test session. Three other reports have presented retrospective observations on the acute effects of MDMA intake by recreational users. Among 100 undergraduate students who completed questionnaires in the study by Peroutka et al. (1988), the most frequently reported effect was the sense of closeness to other people (90%). Effects with negative potential e.g. with respect to increased risk of accidents, reported by more than 20% of the respondents, were difficulties in concentration, dizziness or vertigo, visual hallucinations and drowsiness. Among 100 Australian drug users who completed questionnaires on previous experiences with drugs of abuse (Solowij et al., 1992), the four most frequently reported effects for MDMA were ‘talkative, open minded, closeness to others, and happiness’. The only important negative effect reported with some frequency was poor concentration. Serious negative effects was seldom reported after amphetamine use, while ‘confusion and poor concentration’ was observed after hallucinogen intake. In the third retrospective study, 20 psychiatrists reported the effects they had experienced after previous MDMA use (Liester et al., 1992). The majority of effects reported were considered beneficial, but it should be noted that also possible detrimental effects as altered time perception and cognitive changes were reported with high frequencies. Fifteen per cent or more of the participants also described altered perception of spatial relationships, increased restlessness and agitation, decreased ability to perform mental or physical tasks and disorientation or confusion. Two additional reports have dealt with prospective registration of effects after experimental, controlled administration of MDMA to small groups (20–30) of subjects (Downing, 1986; Greer and Tolbert, 1986). Again the positive effects dominated in the reports. However, a series of undesirable and negative effects was also reported by the subjects participating in the studies, as ataxia, blurred vision, difficulties in walking, brief short-term memory loss, confusion, incoordination, difficulties with multiplication and impaired judgement.

3.2. Medical case histories

There are several medical case reports which have been published on the effects of MDMA intake in usual and in high doses. Many of these reports deal with acute mental and behavioral problems. Recently one of the largest series of MDMA case histories was published (Williams et
This material consisted of consecutive registration of MDMA-related cases seeking medical attendance at the accident and emergency department of St Thomas' Hospital, London, during 15 months in 1995 and 1996. Forty-eight MDMA related episodes among a total of 32,400 attendances in the 15–30 year group were recorded in this period. The majority of cases had consumed between one half to two ecstasy tablets before the episode. The most common clinical features were ‘strange, unwell, dizzy’, ‘collapsed, loss of consciousness’, ‘nausea, vomiting’ and ‘panic, anxiety, restlessness’. There were six severe episodes (delirium, seizures, coma).

There are also several reports in the literature on more serious events. Life threatening and fatal neurological adverse effects as subarachnoid and intracranial haemorrhage, cerebral infarction, and cerebral venous sinus thrombosis have been described, occurring separate from, or together with, a multiorgan syndrome (including hyperthermia); for the review see McCann et al. (1996). Also marked neuropsychiatric adverse effects such as panic disorders, hallucinatory confusion, psychosis and a serotonin behavioral toxic syndrome have been reported in conjunction with MDMA use (McCann et al., 1996).

4. MDMA use and accident risk

Linked to the more severe neuropsychiatric adverse effects, but probably also to milder mental changes, are reports on serious accidents and reckless driving, e.g. a fatal accident after climbing an electrical utility tower (Dowling et al., 1987), five road traffic accidents, two of which were fatal (Henry et al., 1992), a car burn accident (Cadier and Clarke, 1993), a fatal car surfing accident (Hooft and Vande Voorde, 1994), and multiple episodes of dangerous driving after MDMA use (Schifano, 1995). Such reports, although illustrating and scaring, give, however, no indication on how often accident prone behaviour occurs among MDMA users. This question has to be left open until reliable data on the prevalence of MDMA use in the general population, uncomplicated MDMA use among car drivers, and MDMA use among reckless drivers are available.

In the meantime we have studied survey data from Norway on drug use and combined them with data on drug analyses from autopsies and drugged driving cases to obtain an indirect measure of the relative risk of accidents after MDMA use. The National Institute on Alcohol and Drug Research in Norway has by questionnaire yearly asked nation-wide representative samples of young people (15–20 years) on their previous use of drugs. In 1994, 0.3% answered that they had used MDMA once or more, the corresponding figure for amphetamines was 1.1%. In 1998 these figures had increased to 2.6 and 3.7%, respectively. At the National Institute of Forensic Toxicology (NIFT) all analyses of drugs are performed in samples from almost all medico-legal autopsies in Norway. Since 1996 such samples have been screened systematically for the presence of MDMA, which has been found in only 6 cases. In none of the cases was MDMA the only drug found, and only one case represented an accident. In this case MDMA could be considered as contributing to the accident together with other drugs, in the other five cases the role of MDMA in the deaths was unclear.

NIFT also perform all analyses of drugs in blood samples from Norwegian suspected drugged drivers. Norway has the highest detection rate of this type of offence in Europe (Christopherse and Mørland, 1997). These drivers are usually apprehended by the police and subjected to blood sampling subsequent to dangerous behaviour on the road, reckless driving or traffic accidents. Table 1 shows that the number of this type of samples has increased markedly during the last 5 years, and that this is also the case for the detection rate of MDMA and amphetamines in such samples. From Table 1 it can be seen that the relative detection rate of MDMA in blood samples from suspected drugged drivers has increased from 0 to 1.6 over a time period where ecstasy use has been reported to increase 9-fold, according to survey...
Table 1
Drug detection in blood samples from drivers apprehended under the suspicion of drugged driving in Norway

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of samples analysed (approximately)</th>
<th>Percentage with detections</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>MDMA</td>
</tr>
<tr>
<td>1994</td>
<td>2800</td>
<td>0</td>
</tr>
<tr>
<td>1995</td>
<td>3300</td>
<td>0.2</td>
</tr>
<tr>
<td>1996</td>
<td>3200</td>
<td>0.9</td>
</tr>
<tr>
<td>1997</td>
<td>3740</td>
<td>0.8</td>
</tr>
<tr>
<td>1998</td>
<td>4400</td>
<td>1.6</td>
</tr>
</tbody>
</table>

On the other hand, in 1998 when young people reported the use of amphetamines approximately only 1.5 times more often than use of ecstasy, amphetamine was found 20 times as frequently as MDMA in the blood samples from drugged drivers. A likely explanation for this difference could be that the population of MDMA-users was much younger than amphetamine users, and accordingly performed less driving. Another explanation could be that MDMA influenced the users to a lesser extent than amphetamines and thus caused less frequent driving behaviour that would catch the attention of the police. The latter possibility was addressed by comparing blood concentrations of MDMA and amphetamine in samples from apprehended drivers. This comparison was rendered somewhat uncertain due to the frequent presence of other drugs in the samples. We found that 64% of the MDMA positive samples presented drug concentrations equal to or lower than the blood concentrations obtained after intake of a ‘standard dose’ of 100 mg MDMA. In the amphetamine positive group we found that 52% of the samples there were amphetamine concentrations present which were equal to or lower than the blood concentrations obtained after intake of a somewhat high ‘standard dose’ of 75–100 mg pure amphetamine. If we assume that the reason for being apprehended by the police in both groups was deviant behavior in the traffic, the results will, taken together, indicate that MDMA taken in doses used for recreational purposes can lead to influenced driving with a risk comparable to the risk observed after the use of amphetamines in doses, which has been linked to increased accident risk (Logan, 1996).

5. Conclusion

The use of MDMA is accompanied by marked neurobiological changes in the central nervous system, particularly linked to serotonin and catecholamine transmission. A series of possible adverse acute mental and behavioral effects have been observed in people shortly after single dose use of MDMA. More serious complications of such effects have also been reported. The risk of being involved in accidents, particularly road-side traffic accidents, has so far not been determined, but might be comparable to the risk observed for other central nervous stimulating drugs of abuse, such as amphetamines.

References


