Post-Mortem (Re)Distribution of 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"): Human and Animal Data

De Letter, Els; Stove, Christophe; Lambert, Willy; Piette, Michel

In: Current Pharmaceutical Biotechnology, 11 (5), 453-459, 2010

http://www.benthamdirect.org/pages/content.php?CPB/2010/00000011/00000005/0006G.SGM

Review: post-mortem (re)distribution of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"): human and animal data

Els A. De Letter [1], Christophe P. Stove [2], Willy E. Lambert [2], Michel H.A. Piette [1*]

Forensic Institute – Ghent University, Belgium

[1] *Department of Forensic Medicine*
Jozef Kluyskensstraat 29
B- 9000 Gent
Tel: +32 9 264 92 91
Fax: +32 9 264 94 95
[*] corresponding author: Michel.Piette@UGent.be

[2] *Department of Toxicology*
Harelbekestraat 72
B- 9000 Gent

ABSTRACT

In this paper, the distribution and redistribution of the amphetamine derivative, 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) is brought into focus. Animal experimental data were compared with internationally reported MDMA-related human fatalities: in general, these turned out to be parallel with each other.

Due to its inherent properties (e.g. significant volume of distribution), MDMA is liable to postmortem redistribution. Indeed, very high concentrations have been found in cardiac blood and tissues located centrally in the body (blood-rich organs such as lungs and liver in particular). This confirms that post-mortem redistribution due to diffusion from higher to lower concentration can easily take place, mainly at longer post-mortem intervals and when putrefaction occurs. Therefore, we can conclude that for post-mortem quantitation of amphetamine and derivatives, and MDMA in particular, peripheral blood sampling (e.g. femoral vein) remains compulsory. However, if the latter is impossible, MDMA quantification in a few alternative matrices such as vitreous humour and iliopsoas muscle may provide additional information to come to a reliable conclusion. Furthermore, it should be stressed that – at present – it is impossible to estimate the individual susceptibility to the various possible adverse effects of MDMA, which implies that it is impossible to provide a "safe" or "therapeutic" blood MDMA level. Therefore, in current forensic practice, the post-mortem pathological and toxicological findings should form an entity in order to draw a well-grounded conclusion.

Keywords: ecstasy, MDMA, 3,4-methylenedioxymethamphetamine, post-mortem distribution, post-mortem redistribution, post-mortem toxicology, review

I. Introduction

The detection of toxic substances, in particular of illicit drugs, plays an important role in the forensic inquiry. It is important to point out whether or not a person was under the influence at the very moment of an accident or criminal offence.

Whereas the blood or plasma level of a substance often correlates with recent cerebral effects in a living person, this is not necessarily applicable to the dead due to interfering thanato-chemical processes [1]. Problems include post-mortem degradation, redistribution and sometimes even post-mortem production of a substance. When drug instability is important, falsely decreased levels may be measured or the drug can become undetectable. On the other hand, post-mortem redistribution and/or neo-formation may result in falsely elevated concentrations. The competition between drug instability and redistribution should be taken into account when considering a specific concentration as being therapeutic, toxic or lethal. These post-mortem phenomena have been investigated for several compounds such as ethanol, cocaine, benzodiazepines, barbiturates and antidepressant medication. For ethanol, bacterial post-mortem production has been proven [2], whereas for cocaine, instability is prominent [3]. In addition, the interpretation of cocaine levels may be difficult due to competing post-mortem processes, namely tissue release on the one hand, and chemical and enzymatic degradation of the substance on the other [4,5]. Some benzodiazepines - and nitrobenzodiazepines in particular - are chemically and metabolically very unstable [6]. Post-mortem redistribution into cardiac blood has also been substantiated, for example for barbiturates [7], amitriptyline [8-12] and procainamide [13]. In general, basic, highly lipophilic drugs, with an important volume of distribution (> 3 l/kg) are likely to undergo post-mortem redistribution [14]. To a certain extent, the interference of post-mortem phenomena and – more in particular – of post-mortem redistribution, can be avoided by sampling blood as soon as possible after death from an isolated peripheral vein such as the femoral vein [15]. However, post-mortem diffusion of diphenhydramine and dihydrocodeine out of the bladder into femoral blood has been substantiated [16].

Particular attention to post-mortem toxicological and analytical aspects is provided in a few reviews [17-21].

In addition, since vitreous humour – due to its well-isolated position – is only to a minor extent influenced by autolytic processes, this specimen can be an interesting alternative for toxicological purposes. Moreover, vitreous fluid is simple to sample and not affected by haemolysis. Vitreous humour levels have been studied for various substances such as alcohol [22], morphine [23] and cocaine [24].

Furthermore, in case of severe decomposition, the use of post-mortem samples for toxicology (blood, urine, vitreous humour, and tissues such as liver, kidney) can be seriously hampered. In these

circumstances alternative matrices such as bone marrow or even larvae of insects feeding on the host can be useful [25].

Moreover, the above-mentioned post-mortem issue interferes with the standard question for all substances: is the quantified plasma or blood level within the therapeutic range? Or can the latter induce a toxic state or even death?

Abuse of amphetamine derivatives such as MDMA and 3,4-methylenedioxy-amphetamine (MDA) is an important public issue and fatalities are not infrequent in current forensic practice. Furthermore, several authors discuss the troubles encountered in driving under the influence of MDMA (e.g. [26]). Since amphetamine-related fatalities, including those of MDMA users, are increasingly encountered in medico-legal practice (e.g. [27-33]), fundamental research on these post-mortem phenomena remains required. MDMA is frequently improperly considered as "safe" and providing a "safety ratio" [34] is to our opinion hazardous.

II. Scope

This manuscript reviews the current knowledge of possible interference by the above-mentioned post-mortem phenomena when interpreting a post-mortem 3,4-methylenedioxymethamphetamine (MDMA) blood level. To this end, animal experimental and human data are discussed with focus on the publications referenced in the PubMed and Web of Science databases over the last 10 years. In addition, we provide an overview of the data on the (re)distribution of MDMA, in order to study the relevance of sampling post-mortem specimens, additional to blood and urine, such as several tissues (e.g. liver, kidneys, muscle, brain), hair, vitreous humour and larvae. Furthermore, the question was posed as to whether the post-mortem phenomena relating to MDMA are in line with those for the other amphetamine derivatives.

III. Post-mortem phenomena – thanatological changes applied to MDMA

III.1. Post-mortem degradation

Post-mortem degradation of drugs can be due to chemical decomposition of labile molecules or be the result of metabolic processes [35]. MDMA appears to be stable *in vitro* [36, 37]. In addition, in humans, the metabolism of MDMA to the active metabolite 3,4-methylenedioxyamphetamine (MDA) is only a minor pathway; indeed, formation of the glucuronite or sulfate conjugate metabolites 3,4-dihydroxymethamphetamine (HHMA) and 4-hydroxy-3-methoxymethamphetamine (HMMA) is regarded as the predominant pathway in the MDMA metabolism [38]. MDA as the active metabolite of MDMA is usually encountered approximately at 5-10 % of the corresponding MDMA serum or plasma levels [39, 40]. Even though MDA is still pharmacologically active, it has thus a less important contribution than formerly considered.

III.2. Interference by bacteria

At present, there are no arguments to sustain the hypothesis that MDMA is metabolized post mortem by means of bacteria, in contrast to e.g. nitrobenzodiazepines [41]. However, rabbit experiments indicated that MDMA can be converted post mortem to MDA; it is at present not clear how this reaction takes place (see below, paragraph III.3.1).

III.3. Post-mortem (re)distribution

III.3.1. Animal experimental data

Animal experiments dealing with this issue for amphetamine or its analogues are scarce [42, 43]. Hilberg *et al.* described an experiment in which post-mortem redistribution of amphetamine in the rat was studied [42], with further extrapolation to a few medico-legal cases [44]. Moriya *et al.* demonstrated redistribution of methamphetamine into cardiac blood via pulmonary blood vessels in the early post-mortem period [43].

In the experimental work featured by a multidisciplinary approach at Ghent University (Belgium), the post-mortem problems for MDMA were examined using an experimental rabbit model. In a *first study*, the value of post-mortem vitreous humour MDMA levels was investigated for the purpose of avoiding possible thanato-chemical difficulties such as post-mortem redistribution [45]. First, the pharmacokinetics of MDMA in the rabbit after intravenous (iv) administration were considered. A high volume of distribution (5 l/kg), a high systemic clearance (4.1 l/kg per h) and a relatively short half-life (1 h) were found following iv administration of MDMA. A distinct relationship between the MDMA concentrations in the vascular compartment and the vitreous humour was substantiated. Equilibration between the vascular compartment and the vitreous humour was attained about one hour after intravenous

administration. The ratio of the MDMA concentration in vitreous humour to the MDMA blood level was about 1.1 at 120 and 240 minutes after infusion, which indicates a slight accumulation of MDMA in the vitreous compartment. Moreover, a preliminary thanato-toxicological investigation - in which a post-mortem interval of up to 72 h was considered - demonstrated that MDMA concentrations in cardiac blood increased post mortem, whereas vitreous humour MDMA levels were more stable and thus presumably more representative of the ante-mortem blood concentration.

In addition, the post-mortem stability and (re)distribution of MDMA in the rabbit model were further investigated in order to determine which body fluid(s) and/or tissue(s) after death most closely represent the actual ante-mortem concentration. This *second study* [46] dealt with the distribution of MDMA and its metabolite MDA in different body fluids and tissues of rabbits that were killed 2 hours after iv administration of MDMA. Three groups of rabbits were studied. In the first group (control group), the study was performed immediately after sacrifice and in the second group, the animals were preserved at ambient temperature either 24 or 72 h post mortem prior to sampling. Theoretically, post-mortem increases in cardiac blood levels can occur due to intravascular diffusion out of blood-rich organs such as the liver and the lungs [43]. Therefore, in the third group, ligation of the large vessels around the heart was performed (immediately after killing) and these rabbits were further treated as in the second group. In the first group (control group, sampling done immediately after killing) considerable MDMA concentrations were found in the brain and in both lungs. Our data also pointed to substantial elimination of MDMA by hepatic biotransformation and excretion via the bile in addition to renal excretion. In the second group (post-mortem interval either 24 or 72 h prior to sampling), an increase of MDMA and MDA levels in the liver and the eye globe walls was noted. In the lungs, on the other hand, levels tended to decline as a function of increasing post-mortem interval. MDMA concentrations in cardiac and iliopsoas muscle were fairly comparable, remaining stable up to 72 h after death. A third group, in which the large vessels around the heart were ligated immediately after killing, did not show significant differences in blood and tissue MDMA concentrations when compared with the animals of group 2. Therefore, in the rabbit, post-mortem redistribution of MDMA at the cellular level (viz. by pure diffusion gradient from higher to lower concentrations) is probably more important than its redistribution via vascular pathways. In addition, MDA levels were relatively low in all samples, indicating that this molecule is not a major metabolite in the rabbit, at least within the first two hours after administration. Furthermore, the value of vitreous humour as a reliable post-mortem specimen was confirmed. The distribution and redistribution of MDMA and MDA in rabbit tissues were in line with the data obtained after administration of amphetamine in the rat [42, 47].

Since drug levels can be affected by gastric diffusion when the stomach contains a substantial amount of the drug or by diffusion from the trachea when agonal aspiration or post-mortem regurgitation

of vomit occurs, these phenomena were simulated in another rabbit model (*third study* [48]). Indeed, in humans, MDMA is mostly taken orally and therefore, drug levels can be affected by agonal vomit aspiration or post-mortem regurgitation in the airways when the subject dies shortly after ingestion, and – as a result – the distribution is not yet completed. The influence of the gastric reservoir function [49] and vomit aspiration or regurgitation [50] has previously been proven for ethanol. For MDMA, in the third rabbit animal model, post-mortem infusion of an MDMA solution was performed either in the trachea or in the stomach and the diffusion was studied up to 72 hours after administration [48]. After post-mortem tracheal infusion, MDMA easily diffused not only into the lungs but also in large quantities into the cardiac blood and – to a lesser extent – into the cardiac muscle. MDMA was also found in the closely adjacent diaphragm and in the upper abdominal organs, including the liver and the stomach. Following post-mortem infusion into the stomach, considerable MDMA levels were found in cardiac blood and muscle, both lungs, diaphragm and liver tissue, when the solution was concentrated nearby the lower oesophageal sphincter. However, when the MDMA solution was present deeper in the stomach, MDMA levels were higher in the spleen and liver and relatively lower in cardiac blood and muscle. These results indicate that the diffusion of MDMA out of the stomach contents or aspirated vomit and particularly gastro-oesophageal reflux, can lead to considerable post-mortem redistribution. In both experiments, MDA levels were low or below the limit of quantitation in most tissues, but were substantial in cardiac blood and muscle, lung and diaphragm, thus indicating that MDMA can be converted into MDA even after death. However, the mechanism for the latter is at present unclear.

Entomological data dealing with MDMA are scarce. Goff et al. [51] observed that the period required for completion of the larval development in *Parasarcophaga ruficornis* was significantly shorter for the larvae which were fed on liver tissues from rabbits receiving a single MDMA dose of 67 mg intravenously and this colony had the lowest total mortality rate during development. However, no significant differences were noticed in the duration of the puparial period. Therefore, Goff et al. concluded that this should be taken into account when determining the post-mortem interval by entomological study in MDMA-related fatalities [51].

III.3.2. Human data

In this section the animal experimental data are compared with the human findings. The focus is on MDMA and not on some other amphetamine derivatives. The post-mortem distribution of MDMA (and its metabolite MDA) in the human body was investigated, in order to evaluate which fluid and/or tissue sampled after death most closely represents the ante-mortem concentration. Two different – but complementary – approaches were examined: first, the *thanato-toxicological* approach and second, the *anatomo-pathological/thanatological* approach, with emphasis on *immunohistochemistry*.

III.3.2.1. *Thanato-toxicological data*

Though MDMA appears to be stable *in vitro*, its post-mortem (re)distribution in the body has barely been explored, with the exception of case reports: apart from blood and urine concentrations, only some tissue levels have been reported. An overview of the most relevant post-mortem data found in case reports dealing with MDMA-related fatalities are summarized in Supplementary Table 1 [29, 30, 52-95]. Indeed, at present the interpretation of a specific post-mortem MDMA blood level should be made in the light of the available case reports. Unfortunately, the blood sampling site is often not mentioned, though when it is available, it is indicated. Furthermore, fatalities only providing ante-mortem data (e.g. serum levels) and those in which a quantified post-mortem MDMA blood level is not available, are not included in Supplementary Table 1. In addition, all other amphetamine-related fatalities are not taken into account unless MDMA was part of the quantified toxicological results.

In particular, attention is paid to available MDMA blood (cardiac or peripheral), urine, gastric contents, vitreous humour and tissue levels. For the lungs, preference was given to report the upper lobe MDMA levels as in the lower lobes blood stasis is frequent. Considering tissue levels, those were brought into focus which can be compared in several case reports, i.e. mainly liver, kidney, brain, iliopsoas muscle.

Referring to the available thanato-toxicological literature data (see Supplementary Table 1) – indicating a wide range of concentrations –, the interpretation of the MDMA blood level after death remains a debatable question. Indeed a broad range of concentrations is found, viz. between 0.04 µg/ml [81] and 84.00 µg/ml [92] in femoral blood. In the latter case, a femoral blood level of 84.00 µg/ml is extraordinary as the majority of the blood MDMA levels lies between 0.5 and 4 to 5 µg/ml. Unfortunately, the post-mortem interval in that exceptional MDMA fatality is not indicated.

In this review, concentrations in various fluids (blood sampled at different locations, vitreous humour, urine and bile) and tissues such as cardiac muscle, lungs, liver, kidneys, spleen, iliopsoas muscle, and brain were closely considered in MDMA overdose victims. These data show that high MDMA concentrations can be found in organs such as the brain (i.e. important target organ) [52, 53, 57, 60, 61, 67, 69, 90] and the liver [57, 60, 61, 65, 67, 69, 79, 87, 88, 90]. In addition, in the MDMA-related fatalities,

very high concentrations were found in cardiac blood and tissues located centrally in the body (blood-rich organs such as lungs and liver in particular). The latter confirms that post-mortem redistribution due to diffusion from higher to lower concentration can easily take place, mainly at longer post-mortem intervals and when putrefaction occurs. These findings corroborated the animal experimental data in which post-mortem redistribution of MDMA into cardiac blood was substantiated [46, 48]. These results are also in line with the available literature data for amphetamine (AMP), methamphetamine (METH) and MDA (e.g. [15, 44, 96-104]), which indicated that concentrations in cardiac blood are obviously higher than those in peripheral blood. For example, methamphetamine concentrations measured in the left heart of human fatalities are about two times higher than those quantified in the right heart [103]. Blood collected from the pulmonary vessels sometimes showed concentrations that were many times higher than blood sampled from the heart and, as a result, diffusion out of the lungs into the pulmonary circulation was demonstrated [103]. In addition, significant levels of AMP, METH and MDA have been found in several tissues such as liver and brain, but also in blood-rich organs such as the lungs, which means that these substances are liable to post-mortem redistribution.

Referring to Supplementary Table 1 and our data [30, 60, 61, 105], it is obvious that a peripheral sampling site (such as the femoral vein) is recommended. Toxicologists should be aware of the blood sampling location and whether a peripheral blood sample is available. They should be cautious in their conclusions as to whether or not the quantified level is either toxic or lethal. When peripheral blood samples are not available (due to severe loss of blood, such as in polytrauma), iliopsoas-muscle and vitreous humour could be valuable alternatives. In humans, quantification of 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) in the vitreous humour has only been performed in a few cases [56, 57, 59-61, 64, 69, 82]. However, when advanced putrefaction has occurred, vitreous humour is often no longer available due to dehydration, and iliopsoas muscle levels should be interpreted with caution (see e.g. case 01/158 in [61]: the iliopsoas muscle value was obviously higher than the femoral blood level). In contrast to the rabbit experiments, there are arguments for a direct transvascular redistribution, for example, from the lungs to the cardiac chambers in humans. Moreover, due to the post-mortem processes, the toxicological and autopsy findings should be considered as a whole when drawing the medico-legal conclusions.

MDMA (and MDA) quantification in hair samples are at present rare [52, 70, 90] (see Supplementary Table 1). In addition, these can be an indication of previous use and thus tolerance. Further investigation is necessary to determine whether these analyses can be interesting, e.g. in case of suspicion of an anaphylactic reaction or in the interpretation of a quantified MDMA level in a supposedly regular user.

III.3.2.2. *Anatomo-pathological/thanatological* approach, with emphasis on *immunohistochemistry*.

In most drug-related immunohistochemical studies, the drug-effects are indirectly studied, e.g. by demonstration of rhabdomyolysis [67, 68, 106]. In this review, we will focus on the (re)distribution of MDMA itself and thus in this section, a semi-quantitative visual presentation of the distribution of MDMA in tissues is obtained and correlated with the toxicological findings. The question is posed whether immunohistochemical detection could be either an alternative or a supplementary tool in the forensic inquiry when the toxicological determinations are interfered with or have become impossible. In particular, the brain – being an important target organ for MDMA – may be a challenging matrix for chromatographic extraction due to its high lipid fraction. We reported an immunohistochemical method for the detection of MDMA and MDA in human post-mortem brain tissues and the pituitary gland [107]. The detection method comprises an elaborate amplification of the original signal (antigen-antibody recognition; Catalyzed Signal Amplification; CSA [108]). A distinct positive reaction was observed in all cortical brain regions and the neurons of the basal ganglia, the hypothalamus, the hippocampus, the cerebellar vermis, and the pituitary gland. In the brainstem, relatively weak staining of neurons was seen. It should be noted, however, that immunohistochemical detection is restricted to the fraction bound to tissues, since the unbound fraction is washed out during the preparation procedure. This is a fundamental difference with the toxicological quantitation in tissue homogenates, in which both the bound and the unbound fraction are measured. Yet, the immunohistochemical findings were in line with the toxicological data. This immunohistochemical method can thus be used as evidence of intake of or even poisoning with MDA, MDMA and/or MDEA, and it can serve as an alternative method when the usual samples (mainly blood and urine) are not available for toxicological analysis (for example in polytrauma). However, a drawback is that the currently available antibodies cannot distinguish the closely related amphetamine derivatives (MDA, MDMA and MDEA) from one another. In addition, immunodetection could possibly be used as a basis for further study of the distribution of these amphetamine analogues in the human body, and may contribute to the understanding of their neuro-biological effects. However, as already mentioned, the limitation of the immunohistochemical approach is that in the brain sections, only the tissue-bound fraction can be demonstrated. This constitutes a fundamental difference with the toxicological quantitation in tissue homogenates, in which both the bound and the unbound fractions can be assessed.

IV. Discussion & conclusion

Considering the post-mortem changes applicable to MDMA, it can be concluded that – at present – post-mortem degradation of MDMA is of minor consideration. However, post-mortem distribution and redistribution of MDMA is of major interest, in order to evaluate which fluid and/or tissue sample after death most closely represents the ante-mortem concentration. To that aim, animal experimental and human data were closely considered and compared.

For post-mortem toxicological analysis, whole blood MDMA concentrations are predominantly used. When the corresponding serum MDMA level needs to be estimated, a conversion factor of 0.80 would be appropriate [40]. The question arises whether an MDMA blood level can be toxic or even potentially lethal. Referring to possible thanatological changes, it is not clear whether the observed post-mortem MDMA blood level actually represents the concentration at the time of death. However, referring to the distribution data of MDMA, quantification of this substance in a peripheral blood sample and – if the latter is impossible – quantification in a few alternative matrices such as vitreous humour or iliopsoas muscle can provide additional information to come to a sound conclusion. In fact, the statement of Dowling can be maintained: a blood level of MDMA (or MDEA) in excess of 1.0 µg/ml has the potential to cause or contribute significantly toward death, whereas even levels below approximately 0.6 µg/ml appear to be potentially consistent with a state of MDMA (or MDEA) intoxication [109]. In addition, individual susceptibility should be taken into account in determining whether any given dose of MDMA (or MDEA) can be potentially lethal [109]. On the other hand, Musshoff et al. state that MDMA concentrations of 0.35 – 0.5 µg/ml can be considered as toxic [110]. In Supplementary Table 1, a broad interval of described MDMA levels is shown and this was also substantiated by other authors, e.g. Kaye et al. who found in their 68 cases an interval of 0.03 – 93.0 µg/ml (mean 0.85 µg/ml) [111]. Referring to the reported toxicological data and as Kalant stated: it is not possible to estimate the risk and the true incidence of serious or fatal toxicity due to MDMA [112]. Furthermore, there is a variety of possible mechanisms of death [30, 113]. Or in other words, each individual MDMA-related fatality should be accurately considered and the medico-legal findings should be correlated with the toxicological data in order to come to a well-grounded conclusion.

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