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ORIGINAL ARTICLE

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Post-mortem redistribution of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") in the rabbit

Part I: experimental approach after in vivo intravenous infusion

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Abstract Post-mortem redistribution is known to influence blood and tissue levels of various drugs. An animal model was used in an attempt to elucidate this problem for the amphetamine analogue, 3,4-methylenedioxymethamphetamine (MDMA). Rabbits received 1 mg/kg MDMA intravenously (iv) and were killed 2 h later in order to simulate the state of complete distribution in the body. MDMA and 3,4-methylenedioxyamphetamine (MDA) concentrations were determined in blood, urine, bile, vitreous humour, and various tissues (eye globe walls, brain, cardiac muscle, lungs, liver, kidneys, iliopsoas muscle and adipose tissue) using a high pressure liquid chromatographic (HPLC) procedure with fluorescence detection. In the first group (control group, sampling immediately post mortem) considerable MDMA concentrations were found in the brain and both lungs. In addition, our data indicate the elimination of MDMA by hepatic biotransformation and excretion via the bile. When the animals were preserved either 24 or 72 h post mortem (second group), an increase of MDMA and MDA levels in the liver and the eye globe walls was noticed. In the lungs, on the other hand, they tended to decline as a function of increasing post-mortem interval. MDMA levels in cardiac and iliopsoas muscle were fairly comparable and remained stable up to 72 h after death. In the third group, ligation of the large vessels around the heart took place immediately post mortem, but significant differences in blood and tissue MDMA concentrations between rabbits of group 2 and 3 could not be demonstrated. We therefore conclude that post-mortem redistribution of MDMA at the cellular level (viz. by pure diffusion gradient from higher to lower concentrations) is more important than its redistribution via the vascular pathway. Finally, MDA levels were relatively low in all samples, thus indicating that this is not a major metabolite in the rabbit, at least within the first 2 h after administration.

Keywords 3,4-Methylenedioxymethamphetamine (MDMA) · 3,4-Methylenedioxyamphetamine (MDA) · Iv infusion in rabbits · Tissue distribution · Post-mortem redistribution

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Introduction

For many drugs there is a correlation between plasma concentration and pharmacological effect. However, the interpretation of post-mortem concentrations of many substances differs substantially from in vivo quantified levels. In particular, post-mortem instability and redistribution can be important interfering factors, as has been demonstrated for example, for ethanol [1] and also barbiturates [2], cocaine [3], and dothiepin [4]. Post-mortem distribution has also been investigated for more scarcely encountered substances in forensic practice such as laudanosine [5] and dichloromethane [6].

These thanato-chemical problems have barely been explored for the amphetamine analogue, 3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy"), except in a few case reports [7, 8, 9, 10]. For amphetamine and methamphetamine, more literature data are available, e.g. [11, 12, 13, 14, 15, 16, 17, 18, 19]. Animal experiments dealing with this issue for amphetamine or its analogues are scarce [20, 21, 22]. To our knowledge, post-mortem redistribution of MDMA has not been thoroughly investi-

gated either in humans or in animal models. Substances having an apparent volume of distribution of more than 3–4 l/kg are liable to post-mortem drug redistribution [21]. As shown in a previous study using rabbits, MDMA has a volume of distribution at steady state of 4.9±2.6 l/kg [23]. Furthermore, we demonstrated that MDMA concentrations in cardiac blood increased post mortem and that vitreous MDMA levels were more stable [23]. As a result, since substantial post-mortem redistribution of MDMA is suspected and thus could be important to deal with and to take into account when drawing conclusions in current forensic practice, two experiments have been set up. In the first part, death in a state of complete absorption of the drug (e.g. when somebody dies due to multi-organ failure) was simulated. In the second experiment in rabbits [24], post-mortem redistribution was investigated reflecting someone dying due to MDMA ingestion (e.g. due to cardiac arrhythmia) before complete uptake took place and therefore a considerable "reservoir" of the substance is still present in the stomach. Both animal experiments investigated the consequences of sampling and interpretation of the toxicological data, mainly when peripheral blood is not available for analysis.

In this study, the tissue distribution of MDMA and its metabolite 3,4-methylenedioxyamphetamine (MDA) was studied in the rabbit 2 h after intravenous administration. Thereafter we investigated the mechanism of the increases in heart blood MDMA levels, in particular, the redistribution of MDMA from the surrounding tissues into the cardiac blood. Blood and tissue levels were compared both with and without ligature of the large vessels around the heart up to 24 and 72 h after death. One could expect that by simple diffusion across concentration gradients via vascular pathways, blood-rich organs such as the lungs and the liver could contribute to post-mortem increases in drug concentrations in cardiac blood [2].

Materials and methods

The study protocol was approved by the Ethics Committee for Animals of the Medical School, Ghent University (request number ECP 99/20).

MDMA hydrochloride for the rabbit experiments and pure standards (MDA and MDMA) were provided by Sigma-Aldrich (St. Louis, Mo.).

Animals and procedures

Female white New Zealand rabbits (weight 2,000–2,350 g) were purchased from Iffa Credo, Belgium. The animals were fasted overnight before the experiment but were allowed free access to water.

The study design is presented in Fig. 1. Fifteen rabbits received 1 mg/kg MDMA, slowly infused via the left ear vein, and 2 rabbits received a comparable amount of saline and were used as blanks. Blood was sampled after 2 h via the right ear vein (3 ml) for determination of whole blood and serum MDMA levels. Three groups of rabbits were randomly created. In three rabbits (group 1), all samples were immediately taken after death (controls). The remaining 12 rabbits were left in a supine position at an ambient temperature of 18°C and divided into groups 2 and 3, according to whether or not immediate post-mortem ligation was carried out on all the large vessels around the heart. Groups 2 and 3 were each di-

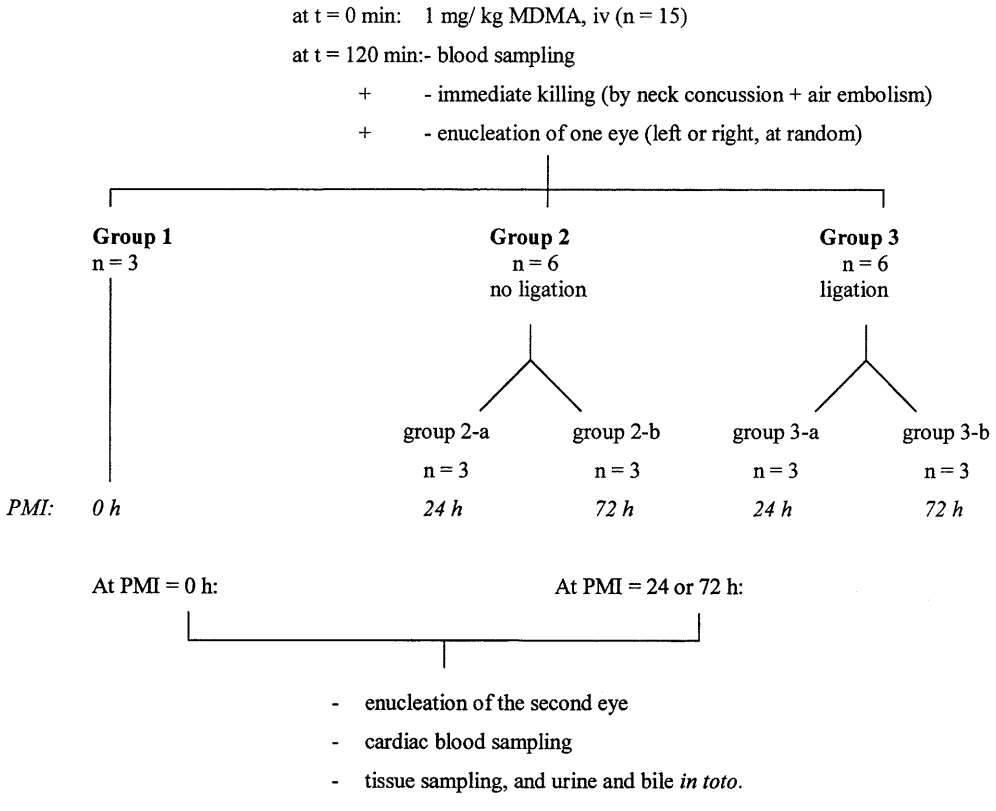


Fig. 1 Scheme of the study design in rabbits receiving 1 mg/kg MDMA iv (*PMI* post-mortem interval expressed in hours).

vided into two subgroups (n=3), which were preserved either 24 h (group a) or 72 h (group b) post mortem. From each rabbit, cardiac blood and the following tissues were sampled: cardiac muscle, right and left lungs, liver, kidney (mixture of right and left), cerebrum, cerebellum, brainstem, stomach wall and stomach content, abdominal adipose tissue, and iliopsoas muscle. In addition, enucleation of the second eye and sampling of urine and bile in toto was carried out. The eyes were handled as previously described [23]. The individual eye globe walls, consisting of the retina, choroidea and sclera, were also preserved for toxicological analysis. In order to avoid contamination of these eye globe walls, all inserting muscle fragments were carefully removed. Aqueous humour, cornea and lens were not included in our protocol. As creatinine is a stable parameter post mortem [25], these levels were determined in the vitreous humour samples and the ratio of MDMA to creatinine concentration was calculated. All samples were stored at –30°C until analysis.

Analytical methods

Drug assay

The samples were analysed using a fully validated procedure developed in our laboratory for the analysis of MDA, MDMA and 3,4-methylenedioxyethylamphetamine (MDEA) [26], [10] in biological matrices. Tissue samples were homogenised after a 1:4 dilution in water using an Ultra-Turrax homogeniser from IKA (Staufen, Germany). The resulting homogenates or biological liquids (serum, whole blood, vitreous humour, urine, bile and stomach content) were liquid/liquid extracted with hexane/ethyl acetate (7:3, v/v) at an alkaline pH of 9.5 (using K_2CO_3). For the tissues, the organic layer was transferred to a test tube containing 1 ml of 1 M HCl. After mixing, the organic layer was discarded. The aqueous layer was adjusted to pH 9.5 (using K_2CO_3) and again extracted with hexane/ethyl acetate (7:3, v/v). The organic layer was evaporated after the addition of 50 µl methanolic HCl.

For the chromatographic separation, a narrow-bore (2.1×150 mm, particle size 3 µm) Hypersil BDS C_{18} column was used with a gradient elution using 0.1 M ammonium acetate in water and acetonitrile/methanol. Fluorescence detection was used with excitation and emission wavelengths of 288 and 324 nm, respectively.

Calibration curves were prepared in the corresponding blank matrix and extracted using the general isolation procedure. When the concentration of an unknown sample exceeded the calibration interval, it was reassayed in an appropriate dilution.

The limit of quantitation (LOQ) for MDMA and MDA was 2 ng/ml for whole blood, serum and vitreous humour, 10 ng/g for tissue samples and 0.1 µg/ml for urine.

Quantitation of creatinine

Creatinine measurements were performed on a Cobas Mira (Basel, Switzerland) automated analyser and were based on the Jaffé reaction (reaction of creatinine and picrate in alkaline medium) [27].

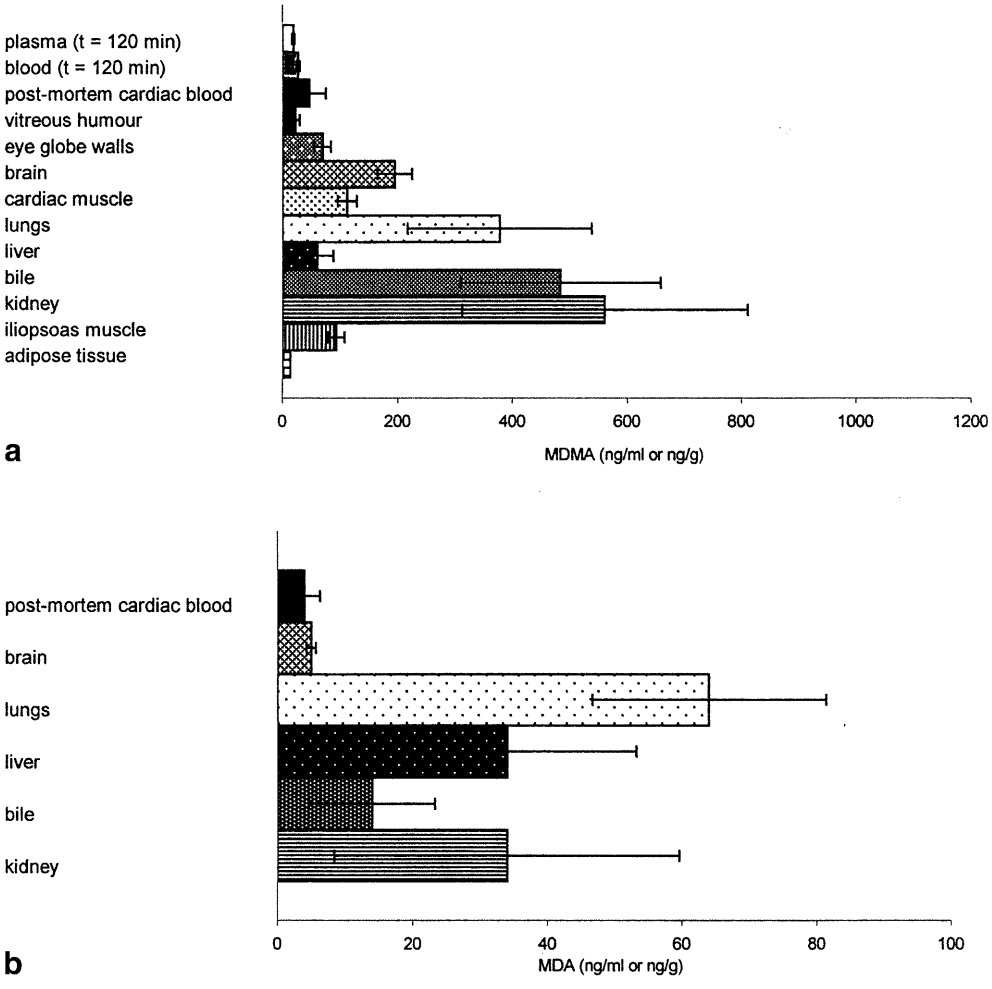


Fig. 2 Mean MDMA **a** or MDA **b** concentrations in blood, vitreous humour, bile and tissues in rabbits after an iv injection of 1 mg/kg MDMA. Sampling occurred 120 min after infusion or immediately after killing (*group 1*, n=3). (Values expressed as mean ± SD)

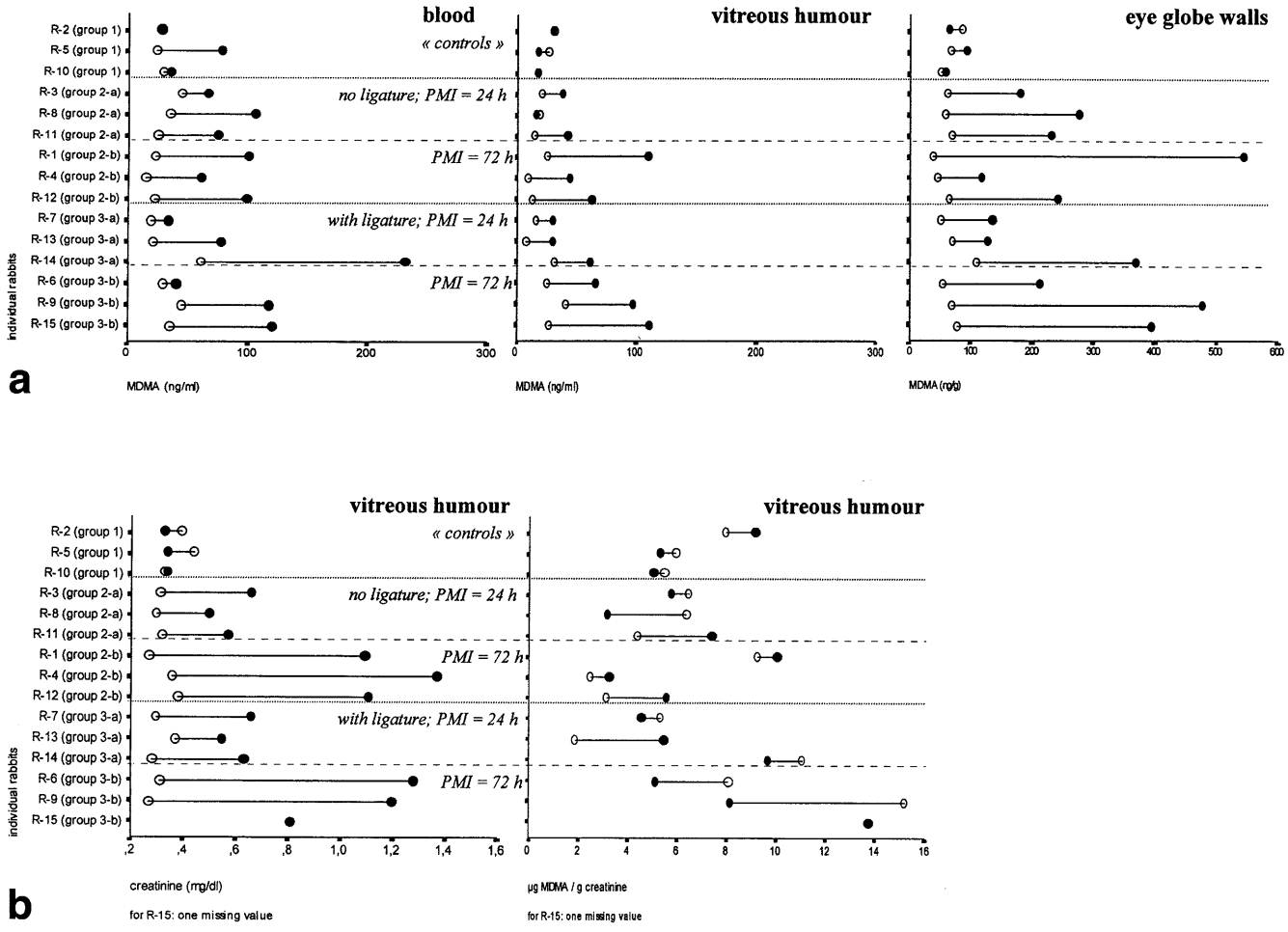


Fig. 3a Individual MDMA concentrations in blood, vitreous humour and eye globe walls after iv injection of 1 mg/kg in rabbits (R) of groups 1, 2 and 3. **b** Individual creatinine concentrations (mg/dl) and individual ratios of MDMA to creatinine concentrations in vitreous humour in rabbits (R) of groups 1, 2 and 3. The first (open circle) and second (closed circle) point represent the ante- or peri-mortem and post-mortem values, respectively, at a particular post-mortem interval

Analysis of data

Statistical processing of the data was performed using non-parametric tests (using the computer programme SPSS, version 10.0 for Windows). The Wilcoxon Rank test was used both for the analysis of intra-individual differences in concentrations between cerebrum, cerebellum and brainstem and for comparing the values of the right and the left lung. The Wilcoxon Rank test was also used to compare the individual vitreous humour and blood MDMA levels. The Mann-Whitney U-test was used to compare the values of groups 2 and 3. The Kruskal-Wallis test was applied to compare the MDMA and creatinine values as a function of post-mortem interval and, when appropriate, this was followed by the Mann-Whitney U-test. The correlation between blood and vitreous humour or tissue MDMA levels was investigated with the Spearman correlation test. For all tests, *P* values less than 0.05 were considered to be statistically significant.

Results

Figure 2 shows the mean concentrations of MDMA and MDA in different tissues of the rabbits of group 1. The MDMA and MDA levels in blood and plasma 120 min after infusion are comparable with those in a previous study [23]. The individual values of the cerebrum, cerebellum and brainstem were taken together as there were no statistically significant differences. The mean of these levels is presented as MDMA concentration in the brain. For the same reason, the mean value of both vitreous humour samples, both eye globe walls and both lungs was used. When compared with the blood level, the highest MDMA concentrations were retrieved in the lungs, the bile and the kidneys, followed by the brain. The MDMA levels in cardiac and iliopsoas muscle were comparable, but were higher than cardiac blood levels. In contrast, the MDMA levels in adipose tissue were mainly below LOQ and only quantifiable in one rabbit. The MDA concentrations were low in blood and in all tissues (<100 ng/g), and only substantial in the lungs, liver, bile and kidney (see Fig. 2b).

In Figure 3, the individual MDMA concentrations in blood, vitreous humour and eye globe walls of groups 1, 2 and 3 (Fig. 3a) are presented. For group 1, the vitreous humour concentration of each individual eye is presented

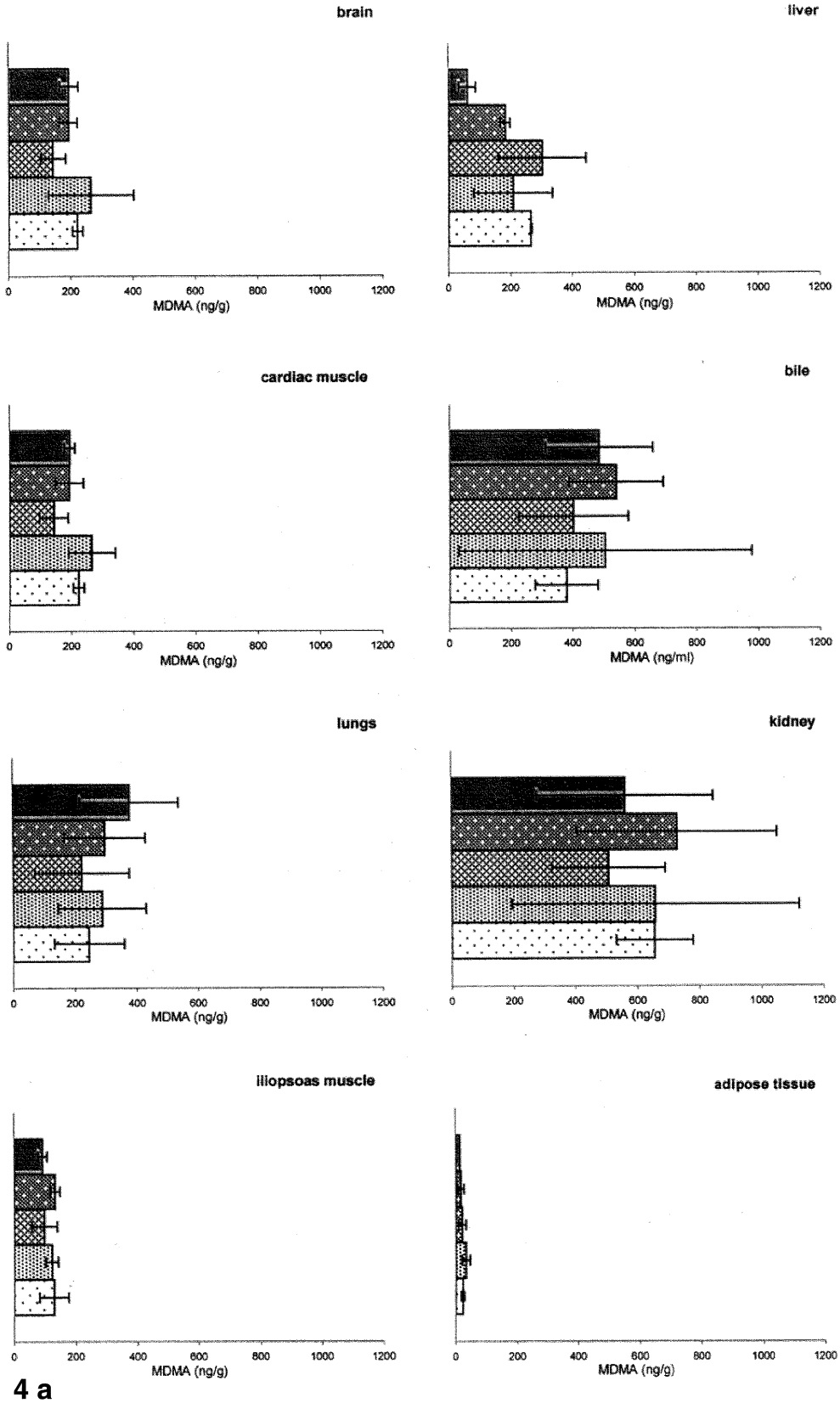
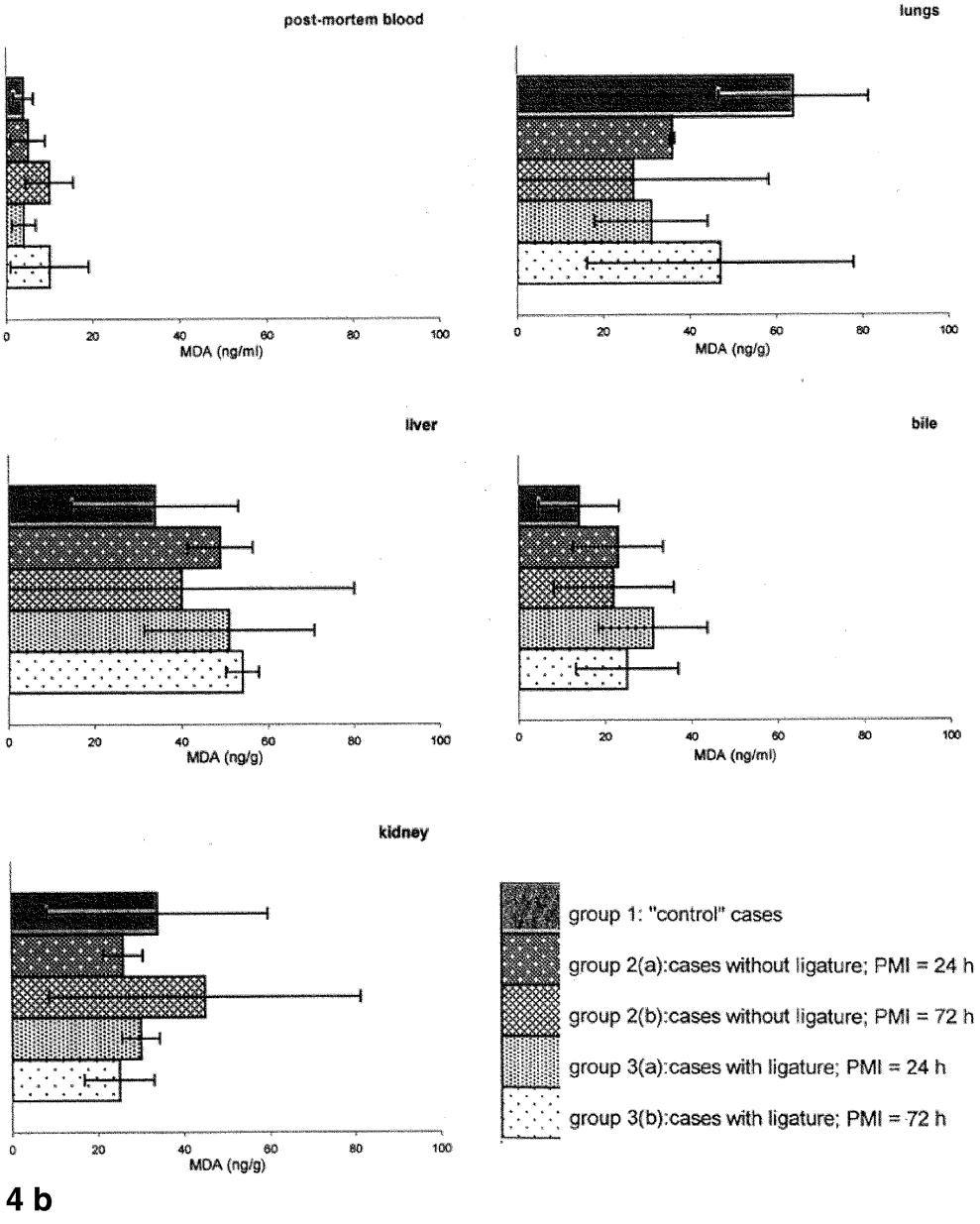


Fig. 4 Mean post-mortem MDMA **a** or MDA **b** concentrations in rabbit tissues after iv injection of 1 mg/kg MDMA. (Values expressed as mean ± SD)

Fig. 4b



4 b

(and not the mean value of both eyes as in Fig. 2). The Wilcoxon test showed that the post-mortem MDMA blood levels differed significantly from the MDMA vitreous humour levels (p=0.006; the blood MDMA concentrations were higher than the corresponding vitreous humour levels). The outlier in the blood MDMA levels (R-14) is not relevant, as contamination with thoracic cavity fluid during sampling occurred. The Kruskal-Wallis test showed significantly different MDMA concentrations for the vitreous humour and the eye globe walls of the second sampled eye (p=0.006 and 0.023, respectively), immediately post mortem and 24 h or 72 h after death. In addition, the individual creatinine concentrations and the ratio of the MDMA to creatinine concentration in vitreous humour are shown (see Fig. 3b). The Kruskal-Wallis test showed statistically significant differences also for the creatinine values in the second sampled eye (p=0.002), immediately post mortem and 24 h or 72 h after death. The results of all Kruskal-Wallis tests were confirmed by the Mann-Whitney U-test. However, no statistically significant differences were found when the ratios of MDMA to creatinine concentration were considered. The Spearman correlation coefficient (r_s) for the MDMA concentration in the vitreous humour and the eye globe walls of the second eye was 0.64 (p=0.05).

In Figure 4, the mean MDMA (see Fig. 4a) and MDA (see Fig. 4b) concentrations in blood and various tissues of groups 1, 2 and 3 are presented. No statistically significant differences between the ligated and non-ligated rabbits were found, either for the MDMA or for the MDA concentrations. The Kruskal-Wallis test, used to compare the values as a function of post-mortem interval, was only significant for the MDMA concentrations in the liver (p=0.015). The Mann-Whitney U-test confirmed a signif-

icant rise in MDMA liver levels 24 h and 72 h after death. The r_s for the MDMA level in post-mortem blood related to cardiac muscle, lungs or liver was 0.64, 0.63 and 0.59, respectively. These correlations were significant at the 0.05 level.

The MDMA concentration in urine, available in 12 rabbits, varied between 500 and 8100 ng/ml. In all rabbits, MDA concentrations in blood and plasma sampled 2 h after infusion, as well as in the vitreous humour and eye globe walls of the first and second sampled eye, were very low (<15 ng/g) or below LOQ. MDA could not be quantified in cardiac or iliopsoas muscle, or in adipose tissue. In the brain, MDA was mainly below LOQ, except for one rabbit (13 ng/g). However, relatively high MDA levels were found in the lungs, the liver, the bile and the kidneys (see Fig. 4b).

Discussion

In the control group (group 1, sampling immediately post mortem), MDMA concentrations were obviously higher in the brain and both lungs than in blood, thus indicating accumulation of the substance in these tissues. The MDMA levels in cardiac and iliopsoas muscle were relatively similar but also higher than in blood, thus indicating potential binding of MDMA to these tissues. The importance of cardiac muscle levels in post-mortem toxicology has previously been investigated extensively, for example for digoxin [28]. Liver MDMA concentrations were relatively low and MDA levels relatively high when compared with the corresponding blood levels. These findings point to hepatic biotransformation and excretion via the bile. To our knowledge, the metabolism of MDMA in rabbits has not yet been elucidated, but in humans, pathways including demethylation to MDA and glucuronide and sulphate conjugation have recently been described [29, 30]. Furthermore, biliary excretion of amphetamine and methamphetamine in the rat was established many years ago [31]. The MDMA concentrations in the kidney were the highest of all, but as the kidney tissue itself is extensively permeated by urine, these levels can be interpreted as due to "inherent contamination". The MDMA levels in adipose tissue were very low and often near or just below the quantification limit. We cannot exclude the possibility that sampling 2 h after iv infusion provides insufficient time for MDMA to gain access into this tissue. As the ratio of the tissue MDMA levels to blood concentrations in our rabbits is higher than 1 for most organs, accumulation of this substance in tissues is established. When we compare our data with the tissue distribution of amphetamine in the rat [21], we notice that the ratios of tissue to blood concentrations of MDMA in the rabbit are higher than the corresponding ratios for amphetamine in the rat, thus indicating that the binding of MDMA is more pronounced than that of amphetamine. In rats, tissue concentrations 2 h after iv administration of (+)-methamphetamine were highest in the kidney, followed by brain, liver and cardiac muscle [32]. Methamphetamine concentrations in rabbit liver after iv infusion were also relatively low and even lower than in skeletal muscle [33].

As the pKa of MDMA is 10.38 [34], MDMA will be found totally in ionised form at physiological pH, and therefore MDMA would not be able to diffuse fluently to the brain. However, referring to the clinical effects, MDMA can easily pass through the blood-brain barrier, a fact which suggests that active transport might take place. A study in mice suggested that P-glycoprotein plays a facilitating role in the entry of MDMA via the blood-brain barrier [35]. In addition, data from rats indicate that metabolites of MDMA (such as glutathione conjugates) enter the brain via a transporter and are subsequently metabolised to thioether conjugates which contribute to the serotonergic neurotoxicity [36, 37]. The rapid partitioning of (+)-methamphetamine in the rat brain was also partially explained by other physicochemical properties (such as small molecular weight) of that substance [32].

Our results confirm the findings of our first study that post-mortem vitreous humour MDMA concentrations are more stable than cardiac blood levels [23]. Referring to the positive correlation between the MDMA levels in post-mortem blood and cardiac muscle, lungs and liver, we can assume a post-mortem diffusion between these organs and cardiac blood. In addition, a significant increase in MDMA concentrations was noted in the homogenates of the eye globe walls sampled in relation to the post-mortem interval. The reliability of creatinine concentrations in post-mortem vitreous humour was substantiated many years ago [25]. The rise in creatinine concentration in vitreous humour at increasing post-mortem interval due to dehydration has been confirmed. As the ratios of MDMA to creatinine concentration still show a tendency to increase (though not statistically significant) at longer post-mortem intervals, the (relatively minor) increases in MDMA vitreous humour levels cannot be due exclusively to dehydration. Indeed, bearing in mind the very high MDMA levels in the globe wall of the second sampled eye and the significant correlation between the vitreous humour and globe wall concentration of that particular eye, it can be assumed that diffusion out of these "reservoirs" into the vitreous humour can occur, and that it will occur mainly at longer post-mortem intervals.

Our data are unable to support the findings of Moriya et al. [20], who demonstrated redistribution of methamphetamine into cardiac blood via pulmonary blood vessels in the early post-mortem period. Indeed, no statistically significant differences between rabbits with (group 3) or without (group 2) ligation of the large vessels around the heart could be substantiated. However, we cannot exclude the possibility that the lack of significant differences between group 2 and group 3 is influenced by the small number of animals.

The bile MDMA levels tended to decrease at longer post-mortem intervals (see Fig. 4a), although these changes were not statistically significant. We believe that the significant increases in post-mortem MDMA liver concentrations can partially be explained as a result of diffusion

from the bile. On the other hand, MDMA concentrations in cardiac and iliopsoas muscle are fairly stable post mortem and can be of interest when the usual toxicological samples (e.g. blood, urine or vitreous humour) are lacking or when advanced putrefaction has occurred. This has previously been suggested for methamphetamine and amphetamine [38].

The MDA levels were relatively low in all organs, being below 100 ng/ml. The highest levels were found in the lungs, liver and bile. The high MDA levels in the lungs indicate either non-specific binding of MDA (in addition to accumulation of MDMA) or local metabolism of MDMA to MDA as the lungs contain enzymes such as cytochromes P450. As MDA could be quantified in the eye globe walls of the second sampled eye in groups 2 and 3 and not in the eyes immediately taken after killing (data not shown), this could indicate that MDA can also be formed post mortem.

Conclusion

In these experiments in rabbits, a state of complete absorption of MDMA was simulated by iv administration. The organ distribution of MDMA and its metabolite MDA was presented and the redistribution up to 72 h post mortem was investigated.

The enhancement of MDMA concentrations in cardiac blood can be due to post-mortem redistribution from the lungs, in the first place, and, to an obviously lesser extent, from the cardiac muscle and liver. As significant differences between rabbits with and without ligation of the large vessels around the heart could not be proven, we believe that post-mortem redistribution on the basis of non-vascular diffusion gradients, namely at cellular levels (from higher to lower concentrations) could be predominant. However, these findings cannot be totally extrapolated to humans due to the different topographic anatomy of the rabbit, where the organs are inherently closer to one another.

This animal study confirms the findings in a recent MDMA fatality [10] that drug concentrations can be influenced by post-mortem redistribution, mainly when sampling takes place centrally in the body. Therefore this phenomenon should be taken into account when drawing medico-legal conclusions, such as whether the MDMA blood concentrations are toxic or potentially lethal. In addition, when an appropriate blood sample is lacking, quantification in the iliopsoas muscle can be helpful to solve the question whether the individual died due to a MDMA overdose.

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