MDMA and MDA Concentrations in Antemortem and Postmortem Specimens in Fatalities Following Hospital Admission

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Abstract

Over the last 15 years, numerous deaths involving “Ecstasy” (3,4-methylenedioxyamphetamine, MDMA) have been reported and described in the literature. In most cases, either antemortem or postmortem concentration data are available. Because of the wide range of results and potential idiosyncratic nature of MDMA toxicity, interpretation of both antemortem and postmortem concentrations is difficult. The possible influence of postmortem redistribution may be an overlooked factor, but existing data involve postmortem concentrations from varying anatomical sites. However, this paper describes for the first time an evaluation of the concentrations of MDMA and 3,4-methylenedioxyamphetamine (MDA) found in five fatalities admitted to hospital where both antemortem and postmortem blood samples were available. Admission MDMA and MDA concentrations ranged between 0.55 and 4.33 mg/L and 0 and 0.10 mg/L, respectively, in antemortem serum/plasma. Postmortem blood MDMA and MDA concentrations ranged between 0.47 and 28.39 mg/L and 0.02 and 1.33 mg/L, respectively. Postmortem concentrations were higher than corresponding antemortem concentrations in all 5 cases with postmortem/antemortem ratios between 1.1 and 6.6 for MDMA and 1.5 and 13.3 for MDA. Differences in concentrations were also observed between anatomical sites, with central sites (e.g., heart) having much higher concentrations than peripheral sites (e.g., femoral). Overall, MDMA and MDA appear to exhibit postmortem redistribution and concentrations measured in postmortem specimens (even from peripheral sites) are not directly comparable with antemortem findings close to or prior to death.

Introduction

3,4-Methylenedioxyamphetamine (MDMA) is a common component of Ecstasy tablets and has been the subject of much scientific debate, particularly with regard to its potential long-term neurotoxic effects (1). Ecstasy use has been reported in social settings such as parties and nightclubs for over 15 years (2). It is invariably ingested by the user to achieve a subjective euphoric state with additional empathic effects (1).

MDMA can exhibit various symptoms including visual hallucinations, confusion, agitation, sweating, coma, and hypotension (3). Other common toxic symptoms include hyperthermia and/or hyponatremia (usually due to excessive water intake), leading to secondary features such as cerebral edema, seizures, organ damage, and ultimately death (3,4). It is also thought that MDMA can precipitate cardiotoxicity in individuals with an existing heart condition (5,6).

MDMA is known to metabolize to 3,4-methylenedioxyamphetamine (MDA) which has also been found to be present in Ecstasy tablets—in addition to MDMA or as the sole constituent (3). The pharmacology of MDMA has been reviewed previously in the literature and indicates MDA concentrations to be significantly lower than the corresponding MDMA concentrations in both plasma and urine (7–9).

Published data have indicated that MDMA concentrations vary in both non-fatal and fatal cases of intoxication (3,4,10,11). This is partly due to recorded variations in the MDMA content in tablets (typically 80–100 mg per tablet), the quantity ingested and any resultant idiosyncratic toxic effects. de la Torre et al. (7) noted a peak plasma MDMA concentration of 0.18 mg/L in 8 healthy volunteers 1.8 h following a single 75-mg oral dose. In addition, the mean peak plasma concentration of MDA was 0.078 mg/L approximately 5 h after administration. Previous studies by Helmlin et al. (8) involved administration of a single oral dose of MDMA of 1.5 mg/kg (equivalent to 105 mg for a 70 kg individual). Peak plasma concentrations of 0.331 mg/L (MDMA) and 0.015 mg/L (MDA) were measured 2 h and 6.3 h post dose, respectively.

Although plasma and serum concentrations above 0.1 mg/L have been associated with instances of hospital admission, following overdosage, concentrations greater than 2 mg/L may be achieved in antemortem plasma and/or postmortem blood (4,10,11).

Early observations in postmortem specimens had suggested that amphetamines are not as prone to redistribution after death as some other drugs are (such as tricyclic antidepressants) (12). There is an increasing amount of data suggesting
that some amphetamine derivatives (in particular methamphetamine and para-methoxyamphetamine (PMA)) may exhibit redistribution to some degree (13,14). With regard to MDMA, Rohrig and Prouty reported a heart (10.9 mg/L) to femoral (2.8 mg/L) blood concentration ratio of 3.89 in one fatality involving MDMA (15). In an extensive study of one particular MDMA case, De Letter et al. (16) showed a left atrial blood to femoral blood ratio of 2.45 with a corresponding ratio of 1.77 for the right atrial blood. A similar study by Dams et al. (17) involving PMA and MDMA presented a left atrial to femoral blood ratio of 1.44 for MDMA and 1.26 for PMA. In the latter study, the greatest differences for both PMA and MDMA were observed in the left pleural blood (ratio of 2.87 to femoral blood for MDMA) and 1.96 (for MDMA) in the pulmonary artery blood (17). Consequently, it has been postulated that redistribution of MDMA is likely to be due to diffusion from the lungs, heart and in certain circumstances, the stomach (16,17).

Despite the usefulness of such studies, existing distribution and redistribution data for MDMA are mainly based on comparison of concentrations between anatomical sites and have not yet involved comparison of antemortem and postmortem concentrations. This paper presents for the first time antemortem and corresponding postmortem MDMA and MDA concentrations in five deaths following initial hospital admission. Data from serial collection times for the antemortem samples and varying anatomical sites for the postmortem samples are also reported.

Materials and Methods

Chromatographic equipment

High-performance liquid chromatography–diode-array detection (HPLC–DAD) analysis was performed using a P580 low pressure pump, STH 585 column oven, ASI-100 autosampler, and a UVD340S DAD all from Dionex (Camberley, U.K.). A Waters Spherisorb S5ODC 4.6-mm × 150-mm cartridge column (Eluent, U.K.), protected by a 4-mm × 10-mm guard column of Spherisorb S5ODS2 was used for the analysis. Data acquisition was handled by a Dionex Chromeleon software package with the DAD recording spectral data between 200 nm and 595 nm. A wavelength of 220 nm was used for quantitative analysis.

Materials

Triethylamine phosphate buffer (TEAP, 1.0 M, pH 3.0) was supplied by Fluka (Dorset, U.K.), the HPLC-grade acetonitrile was supplied by Rathburns Chemicals Ltd (Walkerburn, U.K.). The HPLC-grade 1-chlorobutane was obtained from Fisher Scientific International (Loughborough, U.K.). Sulfuric acid was supplied by BDH Chemicals (Poole, U.K.). Norfenfluramine (internal standard) was kindly donated by Servier Laboratories (Wexham, U.K.). MDMA, MDA, and cinchonine (alternative internal standard) were supplied by Sigma-Aldrich (Dorset, U.K.) and were used to prepare reference and calibration standards for the formal identification and quantitation of these drugs in the specimens analyzed. A linear calibration range of 0.1 to 5 mg/L (MDMA) and 0.05 to 2.5 mg/L (MDA) was produced using blank (pre-screened) equine plasma. Internal quality control standards of 0.2 mg/L and 2 mg/L (MDMA) and 0.1 mg/L and 1 mg/L (MDA) were also produced in equine plasma.

Extraction method for biological specimens

For HPLC–DAD analysis, 0.5 mL of internal standard (5 mg/L norephedrine or 2 mg/L cinchonine in 0.2M Na2CO3 solution, pH 10) was added to 0.5 mL of sample/standard followed by 5 mL of 1-chlorobutane extraction solvent in a 12-mL polypropylene tube. After 3 min mechanical shaking and centrifugation at 3500 rpm for 3 min, the upper solvent layer was transferred to a second tube. Drugs were extracted into 100 mL of added 0.05M H2SO4, and after 3 min shaking and centrifugation at 3500 rpm for 3 min, the upper solvent layer was aspirated, and 100 mL of the acid layer was transferred into a vial for injection. The injection volume was 30 mL.

Chromatographic conditions

Quantitative analysis was based on 10% acetonitrile (90% 25 mM TEAP buffer, pH 3) isocratic elution conditions at a flow rate of 2 mL/min. The column temperature was maintained at 25°C.

Additional screening

Additional drug and alcohol screening was performed using HPLC–DAD, immunoassay, and gas chromatography with nitrogen-phosphorus detection (GC–NPD) and flame-ionization detection (GC–FID) as previously described (18). Screening included over 700 compounds including antidepressants, drugs of abuse, antipsychotics, antihistamines, and β-blockers. When available, antemortem or postmortem urine was also analyzed.

Results

Method validation

The calibration curve was linear between 0.1 and 5 mg/L for MDMA and 0.05 and 2.5 mg/L for MDA. Interanalytical precision was determined using internal quality control standards (0.2 mg/L and 2 mg/L MDMA and 0.1 mg/L and 1 mg/L MDA). Mean concentrations of 0.20 mg/L (± 0.01 mg/L 1 SD) and 1.96 mg/L (± 0.06 mg/L 1 SD) for MDMA were calculated (n = 10) with corresponding CVs of 6% and 2%, respectively. Mean concentrations of 0.11 mg/L (± 0.01 mg/L 1 SD) and 1.04 mg/L (± 0.05 mg/L 1 SD) for MDA were calculated (n = 10) with corresponding CVs of 8% and 5%, respectively. The limit of detection was found to be 0.01 mg/L for both MDMA and MDA.

Blood-plasma studies

In order to investigate potential matrix effects associated with using plasma standards to analyze postmortem blood, whole human transfusion blood was fortified with varying amounts of MDMA and MDA (125, 250, 500, and 1000 mg/L MDMA and 62.5, 125, 250, and 500 mg/L MDA). The concentrations of MDMA and MDA were then measured using plasma calibration standards of identical concentrations. The corre-

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sponding blood concentrations were 124, 243, 500, and 1001 mg/L. MDMA and 66, 123, 248, and 496 mg/L MDA. When plotted, the results produced linear correlation lines with $R^2$ values of 1.00. This indicated that antemortem serum or plasma and postmortem blood concentrations could be measured based on plasma calibration standards.

**Case studies**

The MDMA and MDA concentrations measured in antemortem and postmortem specimens in five Ecstasy cases and the calculated postmortem to antemortem concentration ratios are shown in Table I.

**Case 1.** History a 31-year-old male was admitted to hospital following suspected intravenous injection of crushed amphetamine and Ecstasy tablets. He developed malignant hyperpyrexia and later died.

Drug screening detected MDMA (no MDA), amphetamine, and ethanol (94 mg/dL in the admission serum). Antemortem serum collected 45 min prior to death and postmortem blood from the brachial vein were available for analysis. The amphetamine concentration was measured at 0.183 mg/L in antemortem serum and 0.342 mg/L in the postmortem blood (postmortem/antemortem ratio of 1.9). The antemortem serum and postmortem blood MDMA concentrations are shown in the table. The concentration ratio (postmortem/antemortem) of the postmortem MDMA concentration and the antemortem MDMA concentration was calculated to be 1.9 (the same as for amphetamine, in this case).

**Case 2.** History: a 30-year-old male was recovered from a river after a night out drinking. He was admitted to hospital but later died.

Drug screening detected MDMA (no MDA), chlordiazepoxide, and ethanol (245 mg/dL in the admission serum). Antemortem serum/plasma collected within 9–20 h prior to death and postmortem blood from the “trunk” and left arm were available for analysis. The antemortem serum/plasma and postmortem blood MDMA concentrations are shown in the table. The initial antemortem serum specimen collected 20 h prior to death revealed an MDMA concentration of 0.55 mg/L, which decreased to 0.31 mg/L in the antemortem plasma that was obtained 9 h prior to death. The corresponding concentrations in the postmortem samples were both slightly higher than the antemortem concentration nearest to death, resulting in postmortem/antemortem ratios of 1.5 for the “trunk” blood and 1.7 for the blood obtained from the left arm.

**Case 3.** History: a 26-year-old male was found collapsed in the street after having taken several Ecstasy tablets. He was admitted to hospital but later died after suffering hyperpyrexia.

Drug screening detected MDMA, MDA, and paracetamol (less than 10 mg/L) but no ethanol. Antemortem blood collected 1 h prior to death and postmortem blood from the femoral artery and jugular vein were available for analysis. The antemortem blood and postmortem blood MDMA and MDA concentrations are shown in the table. The concentration ratio (postmortem/antemortem) between the postmortem MDMA concentrations and the antemortem MDMA concentration were calculated to be 1.1 (femoral blood) and 1.5 (jugular blood). The concentration ratio (postmortem/antemortem) between the

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**Table I. Antemortem* and Postmortem MDMA and MDA Concentrations and Ratios in Specimens from Five Ecstasy Cases**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sample (and Site)</th>
<th>MDMA Conc. (mg/L)</th>
<th>MDA Conc. (mg/L)</th>
<th>MDMA PM/AM Ratio</th>
<th>MDA PM/AM Ratio</th>
<th>Collection Time in Relation to Death (± days or h and min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>AM serum</td>
<td>1.22</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>– 45 min</td>
</tr>
<tr>
<td></td>
<td>PM blood (brachial)</td>
<td>2.37</td>
<td>1.9</td>
<td>NA</td>
<td>NA</td>
<td>+ 2 days</td>
</tr>
<tr>
<td></td>
<td>AM serum</td>
<td>0.55</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>– 20 h 15 min</td>
</tr>
<tr>
<td></td>
<td>AM serum</td>
<td>0.58</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>– 19 h 0 min</td>
</tr>
<tr>
<td></td>
<td>AM plasma</td>
<td>0.47</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>– 16 h 30 min</td>
</tr>
<tr>
<td></td>
<td>AM plasma</td>
<td>0.36</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>– 14 h 15 min</td>
</tr>
<tr>
<td></td>
<td>AM plasma</td>
<td>0.36</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>– 12 h 15 min</td>
</tr>
<tr>
<td></td>
<td>AM plasma</td>
<td>0.31</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>– 9 h 15 min</td>
</tr>
<tr>
<td></td>
<td>PM blood (trunk)</td>
<td>0.47</td>
<td>NA</td>
<td>1.5†</td>
<td>NA</td>
<td>+ 3 days</td>
</tr>
<tr>
<td></td>
<td>PM blood (left arm)</td>
<td>0.52</td>
<td>1.7†</td>
<td>NA</td>
<td>NA</td>
<td>+ 3 days</td>
</tr>
<tr>
<td>Case 2</td>
<td>AM blood</td>
<td>2.04</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>– 1 h 10 min</td>
</tr>
<tr>
<td></td>
<td>PM blood (femoral)</td>
<td>2.25</td>
<td>1.1</td>
<td>1.5</td>
<td>–</td>
<td>+ 2 days</td>
</tr>
<tr>
<td></td>
<td>PM blood (jugular)</td>
<td>2.99</td>
<td>0.14</td>
<td>1.5</td>
<td>2.3</td>
<td>+ 2 days</td>
</tr>
<tr>
<td></td>
<td>AM serum</td>
<td>4.33</td>
<td>0.10</td>
<td>–</td>
<td>–</td>
<td>– 1 day</td>
</tr>
<tr>
<td></td>
<td>PM blood (left femoral)</td>
<td>7.25</td>
<td>0.21</td>
<td>1.7</td>
<td>2.1</td>
<td>+ 2 days</td>
</tr>
<tr>
<td></td>
<td>PM blood (right femoral)</td>
<td>6.19</td>
<td>0.19</td>
<td>1.4</td>
<td>1.9</td>
<td>+ 2 days</td>
</tr>
<tr>
<td></td>
<td>PM blood (heart)</td>
<td>28.39</td>
<td>1.33</td>
<td>6.6</td>
<td>13.3</td>
<td>+ 2 days</td>
</tr>
<tr>
<td></td>
<td>PM vitreous humor</td>
<td>11.93</td>
<td>0.39</td>
<td>2.8</td>
<td>3.9</td>
<td>+ 2 days</td>
</tr>
<tr>
<td>Case 3</td>
<td>AM serum</td>
<td>1.08</td>
<td>0.03</td>
<td>–</td>
<td>–</td>
<td>– 2 days</td>
</tr>
<tr>
<td></td>
<td>AM serum</td>
<td>0.76</td>
<td>0.02</td>
<td>–</td>
<td>–</td>
<td>– 1 day</td>
</tr>
<tr>
<td></td>
<td>AM serum</td>
<td>0.44</td>
<td>&lt; 0.01</td>
<td>–</td>
<td>–</td>
<td>0 days</td>
</tr>
<tr>
<td></td>
<td>PM blood (femoral)</td>
<td>1.14</td>
<td>0.02</td>
<td>2.6</td>
<td>&gt; 2.0†</td>
<td>+ 2 days</td>
</tr>
</tbody>
</table>

* Abbreviations: AM, antemortem; PM, postmortem; and NA, not analyzed.

† PM/AM ratio based on antemortem concentration nearest to death.
postmortem MDA concentrations and the antemortem MDA concentration were calculated to be 1.5 (femoral blood) and 2.3 (jugular blood), slightly higher than for MDMA.

Case 4. History. A 22-year-old female was admitted to hospital with hypertension following apparent ingestion of approximately 12 Ecstasy tablets.

Drug screening detected MDMA, MDA, and a cocaine metabolite (benzoylcegonine) but no ethanol. Antemortem serum collected 1 day prior to death and postmortem blood from the left and right femoral vein and the heart were available for analysis. A specimen of vitreous humor was also provided. The antemortem serum and postmortem blood and vitreous humor MDMA and MDA concentrations are shown in the table. The concentrations of both MDMA and MDA were higher in the postmortem samples than the antemortem serum concentrations and also showed a difference between the anatomical sites of collection. Relative to the antemortem serum concentration, there was little difference between the resultant postmortem/antemortem ratios for both MDMA and MDA measured in the left (1.7 MDMA, 2.1 MDA) and right (1.4 MDMA, 1.9 MDA) femoral veins. However, the postmortem/antemortem ratios for both the heart blood (6.6 MDMA, 13.3 MDA) and the vitreous humor (2.8 MDMA, 3.9 MDA) were significantly higher.

Case 5. History. A 63-year-old male was found collapsed at home having allegedly ingested four Ecstasy tablets. He was taken to hospital but died two days later following a cardiac arrest.

Drug screening detected MDMA, MDA, cannabinoids, a cocaine metabolite (benzoylcegonine), and ethanol (152 mg/dl in antemortem urine). Antemortem serum collected within 0–2 days prior to death and postmortem blood from the femoral vein were available for analysis. The antemortem serum and postmortem blood MDMA and MDA concentrations are shown in the table. The initial antemortem serum specimen collected 2 days prior to death revealed an MDMA concentration of 1.08 mg/L, which decreased to 0.44 mg/L in the antemortem serum, obtained on the day of death. A very low MDA concentration was measured in the initial antemortem serum (0.03 mg/L), and no MDA could be detected in the serum sample collected just prior to death (limit of detection 0.01 mg/L). The corresponding concentrations of MDMA and MDA in the postmortem femoral blood were both higher than the antemortem concentrations nearest to death, resulting in postmortem/antemortem ratios of 2.6 for MDMA and an estimated ratio of greater than 2 for MDA.

Discussion

Antemortem MDMA and MDA concentrations

In five cases involving Ecstasy ingestion and resulting in fatalities following a period of hospitalization, antemortem MDMA and MDA concentrations measured in admission serum, plasma, or blood samples ranged from 0.55 to 4.33 mg/L for MDMA and from 0.03 to 0.10 mg/L for MDA (detected in three cases). The mean concentrations were calculated to be 1.84 mg/L MDMA and 0.06 mg/L MDA. These findings support the existing data for MDA being present at far lower concentrations than for MDMA (particularly in plasma)—even in those cases where excessive ingestion was suspected. The corresponding low concentrations of MDA (less than 5% of MDMA concentrations) do not suggest that MDA was present in significant quantities in the Ecstasy tablets ingested (if at all). However, no tablets or fragments were available for analysis to confirm this.

The concentrations and clinical presentation (invariably hypertension and cardiac effects) are also consistent with other published cases of Ecstasy ingestion resulting in hospital admission (4,10,11).

Postmortem MDMA and MDA concentrations

In the five Ecstasy fatalities presented, postmortem blood concentrations from varying anatomical sites ranged from 0.47 to 28.39 mg/L for MDMA and from 0.02 to 1.33 mg/L for MDA (detected in three cases). The highest postmortem MDMA (28.39 mg/L) and MDA (1.33 mg/L) concentrations were measured in the postmortem heart blood of Case 4, where 12 Ecstasy tablets had allegedly been ingested. The corresponding concentrations in blood from the left and right femoral veins were far lower (7.25 mg/L MDMA left femoral and 6.19 mg/L MDMA right femoral). This site-dependent concentration suggests that MDMA and MDA both redistributed after death and would be consistent with extensive multi-site published studies indicating higher concentrations in the heart (16,19). Excluding the apparent elevated concentrations in the heart blood, the concentration ranges in more “peripheral” sites (e.g., femoral vein) of all five cases were 0.47–7.25 mg/L MDMA and 0.02–0.21 mg/L MDA. The mean concentrations were calculated to be 2.90 mg/L for MDMA and 0.13 mg/L for MDA. Such concentrations are typical of other reported fatalities involving MDMA (10,11,15–17,19).

Postmortem vitreous humor MDMA and MDA concentrations were found to be 11.93 and 0.39 mg/L, respectively, in Case 4. There has been some suggestion that vitreous humor may provide data equivalent to that of peripheral sites (e.g., femoral vein), however this did not appear to occur in this case (16,20). The concentrations were also higher than those measured in the antemortem serum one day prior to death (4.33 mg/L MDMA, 0.10 mg/L MDA). Therefore, further work is required in order to determine the relationship between vitreous humor concentrations and both postmortem and antemortem blood concentrations.

Relationship between postmortem and antemortem MDMA and MDA concentrations

The ratios between the postmortem MDMA and MDA concentrations and the antemortem concentration were calculated in all five cases. In instances where a number of antemortem samples were analyzed, the postmortem/antemortem ratio was based on the concentrations measured in the antemortem specimen obtained closest to death. Overall, in all cases, both the MDMA and MDA concentrations were higher in the postmortem specimens compared to the antemortem specimens (i.e., all postmortem/antemortem ratios greater than 1). This indicates, assuming there has not been continued absorption of the drug following sample collection, that MDMA and MDA concentrations increase after death irrespective of the anatomical site of
sample collection. Although the postmortem/antemortem ratios were lower in postmortem blood taken from the femoral vessels, the ratios still ranged from 1.1 to 2.6 for MDMA and 1.5 to 2.0 for MDA. In Case 4, there appeared to be little difference in the postmortem/antemortem ratios between the left and right femoral vein.

As previously mentioned, the highest postmortem concentrations were achieved in the heart blood and vitreous humour (both in Case 4). This resulted in postmortem/antemortem ratios of 6.6 (MDMA) and 13.3 (MDA) in the heart blood and 2.8 (MDMA) and 3.9 (MDA) in the vitreous humour.

Initial studies had shown that the concentration differences observed between postmortem blood and antemortem serum or plasma are not solely due to matrix differences during calibration. In fact, in Case 3, antemortem blood was available (as opposed to serum/plasma) and the MDMA and MDA concentrations were still found to be lower than those measured in the postmortem blood.

Conclusions

The measurement of the MDMA and MDA concentrations in five fatalities involving Ecstasy ingestion provides further information for the interpretation of such data in cases where MDMA or MDA is implicated. New data from both antemortem and postmortem specimens in each case have indicated there is an apparent rise in MDMA and MDA concentrations in blood after death, regardless of the postmortem collection site. However, the subsequent increase in concentration may vary depending on the anatomical site, indicating possible redistribution (e.g., from the heart and/or lungs). As postmortem blood concentrations may not accurately relate to the concentrations either at the time of, or prior to death, calculations based on this assumption (i.e., dosage—using the measured postmortem concentration and theoretical volume of distribution information) should not be made. Any resultant estimate of the dose or number of tablets ingested could be incorrect and misleading.

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References