Multidrug Toxicity Involving Sumatriptan

Jessica L. Knittel*, Shawn P. Vorce, Barry Levine, Rhome L. Hughes and Thomas Z. Bosy

Division of Forensic Toxicology, Armed Forces Medical Examiner System, Dover AFB, Dover, DE 19902, USA

*Author to whom correspondence should be addressed. Email: jessica.l.knittel.ctr@mail.mil

A multidrug fatality involving sumatriptan is reported. Sumatriptan is a tryptamine derivative that acts at 5-HT1B/1D receptors and is used for the treatment of migraines. The decedent was a 21-year-old white female found dead in bed by her spouse. No signs of physical trauma were observed and a large number of prescription medications were discovered at the scene. Toxicological analysis of the central blood revealed sumatriptan at a concentration of 1.03 mg/L. Following therapeutic dosing guidelines, sumatriptan concentrations do not exceed 0.095 mg/L. Sumatriptan was isolated by solid-phase extraction and analyzed using liquid chromatography–tandem mass spectrometry in multiple reaction monitoring mode. A tissue distribution study was completed with the following concentrations measured: 0.61 mg/L in femoral blood, 0.56 mg/L in iliac blood, 5.01 mg/L in urine, 0.51 mg/kg in liver, 3.66 mg/kg in kidney, 0.09 mg/kg in heart, 0.32 mg/kg in spleen, 0.01 mg/kg in brain, 15.99 mg/kg in lung and 78.54 mg/45 mL in the stomach contents. Carisoprodol, meprobamate, fluoxetine, doxylamine, orphenadrine, dextromethorphan and hydroxyzine were also present in the blood at the following concentrations: 3.35, 2.36, 0.63, 0.19, 0.06, 0.55 and 0.16 mg/L. The medical examiner ruled the cause of death as acute mixed drug toxicity and the manner of death as accident.

Introduction

Sumatriptan (3-(2-[(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide) (Figure 1) is a prescription drug used in the treatment of migraines and cluster headaches. Available in the USA since 1993, this tryptamine derivative is currently in the treatment of migraines and cluster headaches. Available 5-mathanesulfonamide) (Figure 1) is a prescription drug used

Case report

A 21-year-old Caucasian female was found unresponsive in bed by her spouse. CPR was started but by the time emergency medical services arrived rigor mortis had begun and the victim was pronounced dead. The spouse reported that the decedent had a history of epilepsy, asthma and chronic residual pain subsequent to scoliosis surgical repair. The decedent had not been feeling well the day before and had sought medical attention. At the hospital, she received treatment, prescriptions for carisoprodol and carbamazepine, and was sent home. The spouse stated that she had been breathing when he went to bed at 02:30 a.m. An initial investigation of the scene revealed a large number of prescription medications.

During the autopsy, the decedent displayed no external injuries though small amounts of vomit were found in the trachea and primary bronchi. Both lungs displayed moderate congestion and edema, with the right lung weighing 610 g and the left lung 630 g. The coronary arteries appeared to be normal with <10% luminal obstruction in the left anterior descending artery. The gastrointestinal contents contained undigested food particles. All other findings were unremarkable. Postmortem specimens were submitted for a comprehensive toxicological examination to include volatiles, drugs of abuse and therapeutic medications.

Experimental

Over 3 months, 70 individual patients were treated elsewhere by licensed physicians and treated 83 times for headache. Sumatriptan is a selective serotonin (5-HT) agonist, which acts at the 5-HT1B receptors causing vasoconstriction and inhibiting vasoactive neuropeptides from being released by the trigeminal nerves. The constriction of the cerebral blood vessels is mediated by the 5-HT1B receptors, which are found primarily on the meningeal arteries (2, 3); however, 5-HT1B receptors are also found on pulmonary, coronary and other peripheral arteries (4–6). This widespread distribution of 5-HT1B receptors may help explain the diversity in the adverse effects that are occasionally observed with sumatriptan use. Adverse effects of sumatriptan typically consist of transient drowsiness, sedation, feelings of warmth or cold, dizziness, numbness, vertigo, tingling, headache, heaviness and chest, neck or throat tightness (1–3). However, more serious cardiovascular complications such as coronary vasospasm, hypertension, ischemic colitis, ventricular tachycardia and myocardial infarction have occurred in some patients (1). The adverse effects most commonly occur with subcutaneous administration but have also been observed after single oral and intranasal doses (7, 8). As the dose of any formulation of sumatriptan increases, the risk of an adverse event occurring also increases. Sumatriptan is not recommended for individuals with a history of heart disease, other significant vessel disease, uncontrolled hypertension or recent use of ergot-type or monoamine oxidase inhibiting medications. However, a number of case reports described in the medical literature have revealed that patients with no underlying cardiac conditions can suffer from cardiac events when using sumatriptan (7–13).

The following case report presents the development of a solid-phase extraction and a quantitative liquid chromatography–tandem mass spectrometry (LC–MS-MS) method for sumatriptan in biological specimens. This method was then applied to a postmortem case where sumatriptan was identified as a contributing factor in the death of an individual.

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columns previously conditioned with 3 mL of methanol, 3 mL of deionized water and 3 mL of 0.1 M phosphate buffer (pH 6.0). The samples were allowed to flow through the columns by gravity followed by sequential washes with 2 mL of deionized water, 2 mL of 20% acetonitrile in deionized water and 1 mL of 0.1 M acetic acid. The columns were dried for 2 min, followed by two additional washes the first consisting of 2 mL of hexane and the second, 3 mL of methanol. The columns were dried under vacuum for 10 min. Samples were eluted with 3 mL of dichloromethane/isopropanol/ammonium hydroxide (78:20:2), and the eluents evaporated at 25°C under nitrogen. The dried samples were reconstituted with 50 μL of acetonitrile, vortexed and transferred to autosampler vials.

Specimens were analyzed by gas chromatography mass spectrometry (GC/MS) using an Agilent (Palo Alto, CA) 6890 GC coupled to a 5975 mass selective detector (MS). The GC column was a J&W DB-5MS (20 m × 0.18 mm i.d. 0.18 μm, Rancho Cordova, CA) with helium as the carrier gas maintained at a constant flow of 1.0 mL/min. Two microliters of sample were injected using a 10:1 split, an inlet temperature of 250°C and a 4-mm inlet liner packed with deactivated glass wool. An initial oven temperature of 70°C was held for 1 min, increased at a rate of 18°C/min to 300°C and held for 10 min, for a total run time of 23.78 min. The MS source and quadrupole temperatures were 230 and 150°C, respectively, with the transfer line set at 280°C. Full-scan electron ionization MS data were collected over a mass range from m/z 42 to 550 with an acquisition threshold of 150 counts.

### Quantitative analysis

To 1 mL of samples, calibrators and controls, 50 μL of sumatriptan-d6 working internal standard solution was added for a final concentration of 0.050 μg/L. Following the addition of 2 mL of 0.1 M phosphate buffer (pH 6.0), the samples were vortexed, sonicated for 10 min and centrifuged at 3,000 rpm for 10 min. Solid-phase extraction columns were conditioned successively with 2 mL of methanol, 2 mL of deionized water and 2 mL of 0.1 M phosphate buffer (pH 6.0). The samples were applied to the conditioned columns and allowed to flow through by gravity. When the application was complete, the columns were washed sequentially with 2 mL of deionized water, 2 mL of 0.1 M acetic acid, 2 mL of methanol and dried under vacuum for 10 min. Compounds were eluted from the columns using 3 mL of dichloromethane/isopropanol/ammonium hydroxide (78:20:2). Ten microliters of 10% hydrochloric acid in methanol, 500 μL of methanol, 500 μL of deionized water and 3 mL of 0.1 M phosphate buffer (pH 6.0). The samples were allowed to flow through the columns by gravity followed by sequential washes with 2 mL of deionized water, 2 mL of 20% acetonitrile in deionized water and 1 mL of 0.1 M acetic acid. The columns were dried for 2 min, followed by two additional washes the first consisting of 2 mL of hexane and the second, 3 mL of methanol. The columns were dried under vacuum for 10 min. Samples were eluted with 3 mL of dichloromethane/isopropanol/ammonium hydroxide (78:20:2), and the eluents evaporated at 25°C under nitrogen. The dried samples were reconstituted with 50 μL of acetonitrile, vortexed and transferred to autosampler vials.

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column compartment was maintained at 35°C and the injection volume was set at 3 μL. A gradient elution was performed with 10 mM ammonium formate (mobile phase A) and 20% acetonitrile in methanol with 0.1% formic acid (mobile phase B) at a constant flow rate of 0.35 mL/min. Gradient conditions were as follows: initial conditions of 15% B increased to 40% B over 2.50 min, ramped to 80% B at 2.75 min and held for 0.5 min, ramped to 15% B at 3.5 min and re-equilibrated at 15% B for 2.00 min, for a total run time of 5.5 min.

The MS was operated in positive ESI mode with analysis operated in multiple reaction monitoring (MRM) acquisition mode. Two MRM transitions were monitored for both sumatriptan and internal standard. Source-dependent parameters were optimized by injecting an unextracted 0.500 mg/L sample multiple times and varying different source parameters with each injection. The optimized source-dependent parameters were as follows: desolvation temperature, 450°C; desolvation gas flow, 850 L/h; cone gas flow, 20 L/h; source temperature, 150°C; cone voltage, 25 V; capillary voltage, 3.5 kV and extractor voltage, 3.0 V.

The compound-dependent parameters for the MS-MS were determined using a combined mobile phase and standard infusion. The infusion pump delivered both the 1.00 mg/L standard solution and mobile phase at initial conditions at a constant flow (10 μL/min) directly into the source. The Optimizer auto-optimization program determined the optimal cone voltage and collision energy for each MRM transition. Table I lists the compound-dependent parameters and MRM transitions monitored for sumatriptan and internal standard.

### Method validation

The following parameters were measured for the validation of sumatriptan: selectivity, specificity, linearity, limit of quantitation (LOQ), limit of detection (LOD), upper limit of linearity (ULOL), within- and between-day precision, accuracy, carryover, extraction recovery and matrix effects.

The linear relationship was evaluated by calculating the line of regression of the eight point curve(s) using the least squares method. The minimum coefficient of determination ($R^2$) of the calibration curve must be 0.980 or better. Additionally, each calibrator was back calculated against the generated curve and compared with the theoretical concentrations. The LOD was defined as the lowest concentration for which the MRM transition ratios are within ±20% of the average MRM transition ratio and ±3% of the relative retention time but had no defined relationship to the theoretical spiked concentration. The LOQ and ULOL were defined as the lowest and highest concentration, respectively, that meet all the above criteria and were within ±20% of the theoretical spiked concentration.

The acceptable values of precision, expressed as the coefficient of variance (CV), for each within- and between-day assay must be ≤15%. Accuracy, defined as the percent difference (% diff) between the average calculated concentration and the theoretical spiked concentration, was also evaluated during each extraction. Each control must be within ±20% of the theoretical spiked concentration to be considered acceptable.

Recovery, defined as the amount of analyte lost during the extraction procedure, was calculated by comparing a sample with standard spiked pre-extraction to a sample spiked post-extraction. Matrix effect was determined by comparing a sample spiked post-extraction to an unextracted sample. Ion suppression was noted if the difference in response was negative and ion enhancement if the response was positive.

### Results and Discussion

#### Method validation

The validation data met all acceptable criteria for method validation. Endogenous components and commonly encountered/structurally related compounds did not produce any interference or quantitative issues for the LC–MS-MS analysis of sumatriptan. Using 1/x weighting, the assay was determined to be linear from 0.001 to 0.500 mg/L. No significant ion suppression or enhancement was detected. Recovery values ranged between 55 and 66% for both sumatriptan and sumatriptan-d₆, but were determined to be sufficient at all concentrations of the calibration curve including the LOQ. The validation data including linearity, LOD, LOQ, ULOL, precision and accuracy are displayed in Table II.

#### Case results

Postmortem specimens were screened for volatile substances, therapeutic drugs and drugs of abuse. No ethanol or other volatile compounds were detected in either the blood or the vitreous humor at the cutoff level of 0.02 g/dL. Immunoassay was used to screen the urine for amphetamine, barbiturates,

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<th>Compound-Dependent Parameters</th>
<th>Cone voltage (V)</th>
<th>Collision energy (eV)</th>
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<tr>
<td>Compound</td>
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<tr>
<td>Sumatriptan-&lt;sup&gt;d&lt;sub&gt;6&lt;/sub&gt;&lt;/sup&gt;</td>
<td>302.2/157.0</td>
<td>40</td>
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<td></td>
<td>302.2/251.0</td>
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<tr>
<td>Sumatriptan</td>
<td>296.1/157.0</td>
<td>38</td>
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<td>Linear regression coefficients:</td>
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<td>1. LOD (mg/L):</td>
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<td>2. LOQ (mg/L):</td>
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<td>3. ULOL (mg/L):</td>
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<td>4. Within-day precision (n = 5):</td>
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<td>5. Between-day precision (n = 12):</td>
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<td>6. Accuracy % diff:</td>
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benzodiazepines, benzoylcegonine, cannabinoids, MDMA, opiates, oxycodone, phencyclidine and 6-acetylmorphine. The urine screened positive for opiates with the presence of hydromorphone being confirmed in the urine by GC–MS. No hydromorphone was detected in the blood at a concentration >0.05 mg/L.

Based on the prescription history of the decedent, comprehensive full-scan acid/neural and alkaline drug screens were performed on the urine specimen using GC/MS. Meprobamate was identified in the acid/neural drug screen. Using GC/MS, both meprobamate and carisoprodol were confirmed and quantitated in the blood. The alkaline screen identified fluoxetine, doxylamine, orphenadrine, dextromethorphan and hydroxyzine. The presence of each of these drugs was confirmed in the urine and quantitated in the blood. The quantitative blood results for each of the compounds mentioned above are displayed in Table III. Additionally, nicotine, cotinine, trimethoprim and metabolites or breakdown products of hydroxyzine, dextromethorphan, gabapentin and ondansetron were detected in the urine but not quantitated. Sumatriptan was also identified by the alkaline screen and quantitated in the central blood at a concentration of 1.03 mg/L. Given that the concentration of sumatriptan identified in the decedent’s blood was approximately ten times greater than concentrations reported in the literature for therapeutic use, a tissue distribution study was performed on all submitted postmortem specimens. Blood calibrators were used to quantitate the tissue specimens after preparing tissue homogenates in water. Tissues were diluted to ensure quantitation within the limits of the standard curve. The tissue distribution results are displayed in Table IV.

Review of the sumatriptan concentrations measured in the blood and tissue specimens identifies several areas of interest. First, the two peripheral blood specimens have sumatriptan concentrations ~40% lower than the central blood concentration. Cardiac to peripheral blood ratios (C/P) were 1.68 for the femoral blood and 1.83 for the iliac blood. C/P ratios and volumes of distribution for 113 drugs were published by Dalhe-Scott et al. (15). The C/P ratios and volume of distribution for sumatriptan are comparable to the values reported for amantadine, clonazepam, orphenadrine, thioental and timolol all of which may potentially exhibit postmortem redistribution (1, 15). Second, the lung concentration is an order of magnitude higher than the blood or liver sumatriptan concentrations. The high concentration of sumatriptan in the lung may be due in part to the presence of vomit found in the decedent’s trachea and primary bronchi during autopsy. Vomit in the airways has been associated with postmortem redistribution and specifically an increase in cardiac blood concentrations (16, 17). Moreover, when the drug concentration in the heart blood is greater than that of the myocardium, it has been suggested that redistribution from the lungs has occurred (17). The C/P blood ratios and the presence of vomit in the lungs indicate that postmortem redistribution of sumatriptan has likely occurred. However, additional case reports are required before a more definite statement about postmortem redistribution can be made.

Another area of interest centers around why the liver drug concentration is lower than both the central and peripheral blood concentrations. The liver to central blood concentration ratio is 0.49; while the liver to femoral and iliac blood ratios are 0.83 and 0.91, respectively. Several cases involving tryptamine overdoses have examined liver to blood concentration ratios. In a single overdose case, Sklerov et al. (18) observed a liver to heart blood 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) concentration ratio of 8.7 and liver to peripheral blood concentration ratio of 13.6. Additionally, Boland et al. (19) reported a fatality due to a-methyltryptamine (AMT) with liver to peripheral blood concentration ratio of 12.3. Finally, Morano et al. (20) observed a liver to heart blood ratio of 3.2 in a single ethyltryptamine overdose case.

Based on the autopsy and analytical findings in this case, the medical examiner ruled the cause of death was acute mixed drug toxicity and the manner of death was accidental. While toxic and lethal concentration ranges have not yet been established for sumatriptan, the quantitative results measured in this case were deemed significant to the death as they were considerably higher than the reported therapeutic concentrations. However, the death cannot be entirely attributed to sumatriptan. Dextromethorphan and hydroxyzine were identified at toxic but not fatal levels; while the remaining drugs were identified at therapeutic or subtherapeutic levels. Individually, these drugs may not have caused the fatality but synergistic effects may have occurred, so they cannot be ignored when determining the cause of death.

Funding
This work was funded in part by the American Registry of Pathology, Camden, Delaware 19934.

Conflict of interest
The opinions or assertions presented hereafter are the private views of the authors and should not be construed as official or
as reflecting the views of the Department of Defense, its branches, the US Army Medical Research and Material Command or the Armed Forces Medical Examiner System.

References